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HERNIORRHAPHY IN CIRRHOSIS OF THE LIVER WITH ASCITES*

ROBERT H. YONEMOTO, M.D.,† AND CHARLES S. DAVIDSON, M.D.‡

BOSTON

HERNIA is known to be more frequent among patients with cirrhosis of the liver, especially with ascites, than among those without liver disease. Chapman et al.[1] reported a rate of 10 per cent in 58 patients without ascites whereas among those with ascites, the figure was 23.8 per cent (47 out of 112 cases). Henriksson[2] stated that hernia occurred in 16 per cent (26 out of 162 cases) of patients with cirrhosis (with and without ascites).

It is well recognized that surgical procedures, including herniorrhaphy, are often poorly tolerated when cirrhosis is severe. Thus, poor wound healing might be expected in these patients, who are usually undernourished, have anemia, edema and hypoalbuminemia and who may have leakage of ascitic fluid or bleeding into their wounds. In addition, hepatic coma occasionally follows major surgical procedures, particularly after bleeding and injudicious analgesic and hypnotic administration. Some of the usual anesthetic agents may not be tolerated as well as they are by patients with normal livers. Excessive bleeding is sometimes encountered during and immediately after the operation. However, because of the increased occurrence of hernia and therefore the greater possibility of incarceration, strangulation or spontaneous rupture with drainage of ascitic fluid, it seemed desirable to repair the hernias in patients with cirrhosis whenever necessary and, in any event, as soon during rehabilitation as the patient's condition permitted, in spite of clinical and laboratory evidence of severe liver disease, ascites and undernutrition.

This report concerns 11 patients with severe liver disease under study on the Thorndike Ward who had one or more herniorrhaphies. Sixteen herniorrhaphies were done, 2 patients having coexistent hernias at different sites and 1 having three attempts at repair because of recurrences. With the exception of 1 (Case 7), who had a wound infection after the third procedure, all patients not only survived the operation but also recovered promptly without greatly slowed wound healing, dehiscence, infection, prolonged leakage of ascitic fluid or hepatic coma.

MATERIALS AND METHODS

Eleven patients (10 males and 1 female) who underwent sixteen herniorrhaphies in the years 1949 through 1954 were selected for study. Their ages were between thirty-four and seventy years. All were alcoholics and suffered from severe, chronic, usually stabilized, cirrhosis, established by history, clinical findings and liver-function tests (Table 1). The duration of cirrhosis listed in Table 1 is the time elapsed after the diagnosis of cirrhosis was first made. All had ascites and edema of moderate to severe degree at the time of operation. All but 1 had had abdominal paracenteses — some many times. Except when a complication of the hernia demanded immediate operation, they were treated for the hepatic disease for a considerable period, the signs of liver disease and nutritional status and, presumably, the surgical risk often being somewhat improved.

The laboratory data selected for Table 1 were taken as near to the time of operation as possible. Usually, this was within a week or two, but occasionally the interval was considerably longer. Some improvement in hepatic function was often evident when the patients had been followed for prolonged periods before operation (Fig. 1). Clinical jaundice was present in 6 patients when they were first observed, and cleared in 3.

Total serum bilirubin was determined by the method of Ducci and Watson,[3] and the icteric index by that of Ham.[3] Bilirubinemia by one of these two methods was observed in 5 patients. Bromsulfalein

*From the Thorndike Memorial Laboratory, Second and Fourth (Harvard) Medical and Fifth (Harvard) Surgical Services, Boston City Hospital, and the departments of Medicine and Surgery, Harvard Medical School.

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†Formerly, research fellow in surgery, Harvard Medical School, and research fellow, Thorndike Memorial Laboratory, Boston City Hospital.

‡Associate professor of medicine, Harvard Medical School; associate director, Second and Fourth (Harvard) Medical Services, Boston City Hospital.

retention, which was measured in the serum forty-five minutes after the intravenous administration of 5 mg. of dye per kilogram of body weight,[6] was 19 per cent or above in each case. The serum albumin concentration was determined by the micro-Kjeldahl analysis of fractions separated by the method of Howe.[4] The first albumin value was obtained at the time of admission to the metabolic ward, and the second at about the time of surgery. Considerable improvement was observed when both values were available.

5), in whom this syndrome developed a few hours after surgery, lasting for three days but subsequently clearing. On admission to the metabolic ward this patient had had a similar degree of impending coma, and, therefore, surgery was not carried out until this completely cleared, which required four weeks.

Among the 16 hernias, 9 were umbilical, 4 inguinal and 3 ventral (Table 2). Six preoperative complications were encountered: 4 cases of incarceration, and 1 each of strangulation and spontaneous leakage of

TABLE 1. *Severity of Liver Disease and Nutritional Status.*

Case No.	Age	Sex	Duration of Cirrhosis	No. Taps for Ascites	Duration of Ascites	Edema	Icteric Index*			Serum Albumin§	Hematocrit	Nutritional Status	Signs of Impending Coma
							Jaundice	Serum bilirubin (total)†	Bromsulfalein retention‡				
	yr.				mo.			mg./100 ml.	% in 45 min.	gm./100 ml.	%		
1	70	M	2½ yr.	12	3	++	Negative	0.35	24	2.5 to 3.8	33	Fair	None
2	46	M	½ mo.	3	¼	+++	+	25	43	2.0 to 2.9	32	Fair	None
3	53	M	3 yr.	Multiple (every 2 wk.)	36	++++	Negative	10	32	2.0 to 2.8	34	Poor	None
4	62	M	1 yr.	3	½	++++	Negative	12.5	40	2.6 to 3.6	21	Fair	None
5	34	M	10 mo.	0	10	+++	+	7.0		1.6 to 2.6	33	Poor	Mild confusion, tremor
6	67	M	2 mo.	2	2	+++	Negative	2.60	44	1.9 to 2.2	35	Fair	None
7	49	M	8 mo.	4	8	++	++	1.8	35	2.6	40	Fair	None
8	53	M	1 yr.	20	12	++++	+++	0.67	26	1.5 to 3.0	37	Poor	None
9	64	M	6 mo.	5	6	++	+	1.7	46	? to 2.5	31	Good	None
10	58	F	1 yr.	3	12	++	±	0.96	25	2.4 to 2.9	39	Poor	None
11	56	M	6 mo.	2	6	++	Negative	0.86	19	to 3.9	36	Fair	None

*30-min. centrifugation at 3000 r.p.m., compared with standard, by method of Ham.[3]
†Normal range, 0.1-0.8 mg./100 ml.
‡5 mg. per kilogram of body weight injected intravenously; normal range, 1-5 per cent.
§Micro-Kjeldahl analysis of fractions separated by method of Howe[4]; 1st figure represents level on admission, & 2d that about time of surgery.

The nutritional status was graded according to history of loss of flesh and clinical evidence of subcutaneous tissue decrease and muscle atrophy and was considered to be poor in 4 patients, fair in 6 and good in 1. Mild to moderate anemia as judged by hematocrit was present in all. Hematemesis and melena were not known to have occurred except in 1 patient (Case 9), who had three days of rectal bleeding two weeks before operation that spontaneously ceased. In spite of the severe liver disease none of the patients had signs of impending hepatic coma except 1 (Case

ascitic fluid. Emergency surgery was necessary in all these patients with complications except for the last (Case 1), who had leakage of ascitic fluid from a thin-walled umbilical-hernia sac that had ulcerated and become infected. For this patient sterile pressure dressings were applied preoperatively, paracentesis was carried out to reduce intra-abdominal pressure, and antibiotics were administered. Within a week the infection had cleared, and leakage of ascitic fluid ceased. Four weeks later herniorrhaphy was carried out.

One patient (Case 3) presented clinical evidence of strangulation and was found at operation to have discoloration and a subserosal hematoma in the wall of the upper jejunum, which was incorporated in the hernia. Observation for several minutes revealed noticeable improvement in circulation so that the bowel was not resected. He did well postoperatively. Tuberculous peritonitis was discovered at operation in 1 case.

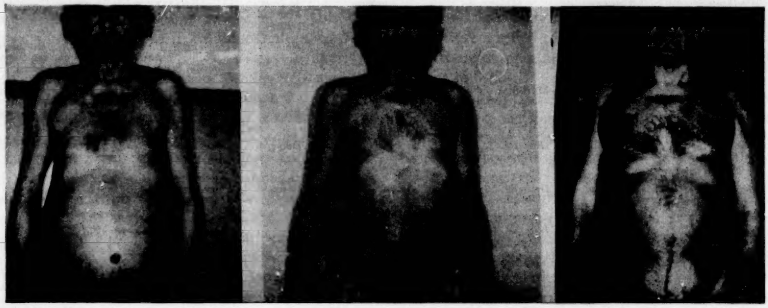

FIGURE 1. *Improvement in Appearance before Operation.*

RESULTS

Preoperative Preparation and Postoperative Care

Preoperative treatment, which usually was a part of the prolonged metabolic study and control of ascites and edema formation,[7-9] consisted of providing an adequate diet, restricted to 200 mg. of sodium daily. This regimen prevented further accumulation of ascites. As previously observed in this laboratory, diuresis with loss of ascites and edema was often delayed for many months or even longer after sodium restriction was begun.[7] Herniorrhaphy was postponed as long as practicable while this regimen was carried out (Fig. 1).

TABLE 2. *Site of Hernia and Complications.*

SITE	PATIENTS WITH NO COMPLICATION	PATIENTS WITH STRANGULATION	PATIENTS WITH INCARCERATION	PATIENTS WITH SPONTANEOUS LEAKAGE	TOTALS
Umbilical	4	1	3	1	9
Inguinal	4	0	0	0	4
Ventral	2	0	1	0	3
Totals	10	1	4	1	16

Mercurial diuretics were sometimes administered although they were often not effective in stimulating diuresis. Blood transfusions were occasionally given to patients with severe anemia in preparation for surgery. Hypoalbuminemia was not further treated by the administration of plasma or serum albumin.

The postoperative care did not differ from the preoperative except that attention was given to possible strain of the suture line; therefore, control of ascitic-fluid formation was continued by sodium restriction as before operation. In 1 case paracentesis was necessary postoperatively, but no difficulty resulted. Penicillin was administered to most of the patients for a few days after operation.

Operative Procedure, Anesthesia (Including Preoperative and Postoperative Medication) and Recovery

The type of surgery, anesthesia and subsequent course is shown in Table 3. The usual Bassini repair, with the exception of 1 (Cooper's ligament repair), was used for the 4 inguinal hernias. The umbilical hernias were repaired either by the Mayo technic or by the use of double loops of near-and-far sutures applied so as to include the peritoneum, posterior rectus fascia and anterior rectus fascia as one layer with No. 30 stainless-steel wire.

On patient (Case 3) had three consecutive repairs for hernias of different sites, and another (Case 10) had two herniorrhaphies at different sites. Case 7 had, in addition to an umbilical hernia, two ventral hernias in the upper mid-line with a diastasis recti. The first repair failed two months after the procedure, necessitating the second operation. Because of another recurrence, six months after the second, a third attempt was necessary. By this time considerable weakening of the structure of the abdominal wall with fascial defect had developed, necessitating a tantalum-mesh enforcement. During a follow-up period of five months, no recurrence was seen.

Preoperative medication was omitted for 2 patients, but as a rule atropine and Demerol or phenobarbital were administered in quantities approximately half to three quarters those given to patients without liver disease. Although undesirable, morphine was given inadvertently on one occasion. Of the 16 anesthesias, 11 were spinal (including 1 continuous segmental), 2 local (1 or 2 per cent procaine intercostal nerve

block and regional infiltration), and 3 were endotracheal (2 with cyclopropane and oxygen, and 1 with nitrous oxide and oxygen).

ing in patients with severe liver disease — for example, lowered clotting factors and thrombocytopenia — are not easily correctable, although a standard dose of

TABLE 3. *Types of Operation, Anesthesia and Subsequent Course.*

CASE NO.	SITE OF HERNIA	TYPE OF SURGERY	PREOPERATIVE MEDICATION	ANESTHESIA DURING SURGERY	POSTOPERATIVE MEDICATION	COURSE OF RECOVERY	COMMENT
1	Umbilical	Mayo repair	None	Local	None	Uneventful wound healing; sutures out on 8th day.	Death from bleeding hepatoma 5 mo. after operation
2	Umbilical (incarcerated)	Mayo repair (No. 32 wire)	Morphine sulfate, 10 mg.; atropine, 0.43 mg.	Spinal		Uneventful; sutures out on 8th day.	Death from bleeding esophageal varices 8 mo. after operation
3	Umbilical (strangulated)	Mayo repair	Demerol, 50 mg.; atropine, 0.43 mg.	Spinal	Demerol	Uneventful; sutures out on 7th day.	Strangulation, but resection avoided
	Inguinal (right)	Bassini repair	Demerol, 50 mg.; atropine, 0.43 mg.	Spinal	Demerol	Uneventful	2d operation performed 34 days after 1st
	Inguinal (left)	Bassini repair	Demerol, 50 mg.; atropine, 0.43 mg.	Spinal	Demerol	Uneventful	3d operation performed 10 days after 2d
4	Inguinal (left, sliding)	Repair of Cooper's ligament	Phenobarbital, 45 mg.; atropine, 0.43 mg.; Demerol, 25 mg.	Spinal	Demerol	Uneventful; sutures out on 7th day.	500-ml. blood transfusion before & 500-ml. during operation owing to anemia
5	Umbilical (incarcerated)	Jones type of closure (No. 30 wire)*	Phenobarbital, 30 mg.	Segmental spinal	None	Uneventful; sutures out on 10th day; 3 days postoperatively mild confusion & tremor.	On admission mild confusion & flap; 9000 ml. of ascitic fluid removed at surgery.
6	Umbilical	Mayo repair	None	Spinal	None	Uneventful; sutures out on 9th day.	None
7	Umbilical & ventral (incarcerated)	Jones type of closure (No. 30 wire)*	Demerol, 75 mg.; atropine, 0.43 mg.; Nembutal, 97 mg.	Endotracheal (cyclopropane & oxygen)	Demerol	Uneventful; paracentesis required on 5th postoperative day.	15,000 ml. of ascitic fluid removed at surgery; recurrence 2 mo. later.
	Recurrent ventral	Imbrication (No. 30 wire)	Demerol, 100 mg.; atropine, 0.43 mg.; Nembutal, 97 mg.	Endotracheal (nitrous oxide & oxygen)	Demerol	Uneventful; sutures out on 7th day.	2d recurrence 6 mo. later
	Recurrent ventral	Tantalum-mesh repair	Chloral hydrate, 650 mg.; Demerol, 75 mg.; atropine, 0.43 mg.	Endotracheal (cyclopropane & oxygen)	Demerol	Postoperative hemorrhage in wound followed by infection	During procedure small bowel inadvertently entered, causing contamination; no recurrence as of date of writing.
8	Umbilical (incarcerated)	Layer closure (No. 30 and 20 silk)	Demerol, 75 mg.; atropine, 0.43 mg.	Spinal	Demerol	Uneventful; sutures out on 7th day.	None
9	Umbilical	Imbrication (No. 20 cotton)	Atropine, 0.43 mg.	Local	Demerol	Uneventful; sutures out on 9th day.	None
10	Umbilical (incarcerated)	Layer closure (No. 0 cotton)	Atropine, 0.43 mg.; barbital, 325 mg.	Spinal	Demerol	Uneventful	None
	Inguinal (left)	Bassini repair	Chloral hydrate, 650 mg.	Spinal	Codeine	Uneventful; sutures out on 9th day.	2d operation 3 mo. after 1st
11	Umbilical	Jones type of closure (No. 30 wire)*	Phenobarbital, 65 mg.; atropine, 0.43 mg.	Spinal	Demerol	Uneventful; sutures out on 7th day.	Exploration revealed multiple peritoneal tuberculous implants, with cirrhosis of liver

*One-layer closure including peritoneum, posterior & anterior rectus fascia, utilizing double-loop near-&-far wire suture.

Because excessive bleeding is common and poorly tolerated by patients with severe liver disease, meticulous hemostasis was carried out. Nevertheless, 1 patient bled profusely during operation, and oozing from the wound postoperatively required two transfusions, one during surgery and one afterward. Most of the factors considered to produce excessive bleed-

vitamin K (5 mg. daily) was administered for several days preoperatively.

All the patients had ascites at the time of herniorrhaphy, and usually drainage of ascitic fluid was unavoidable. Because paracentesis is a dehydrating procedure that may lead to oliguria and a rise in blood hematocrit and sometimes to hepatic coma, it

seemed advisable to remove as little ascitic fluid at one time as practicable. Two patients (Case 5 and Case 7, first herniorrhaphy) were relieved of 9000 ml. and 15,000 ml. of ascitic fluid, respectively, during the surgical procedure. This was followed temporarily by signs of impending hepatic coma in Case 5. Considering the fluid and electrolyte disturbances after removal of large volumes of ascitic fluid,[8] this procedure should be avoided by paracentesis as long before operation as possible.

All patients tolerated the operations well and had no hypotensive episodes. The majority received Demerol for postoperative pain. Two required no postoperative analgesics.

Uneventful primary wound healing occurred after each operation, with the exception of Case 7 (third procedure), in whom wound infection developed from contamination after the small bowel had been entered inadvertently. No other wound infection was encountered, nor was dehiscence or prolonged leakage of ascitic fluid observed. All sutures were removed between the seventh and tenth postoperative days.

Follow-up Study

Five out of 11 patients died within a year of their herniorrhaphies, either from bleeding esophageal varices, hepatic coma or hepatoma (Case 1). One patient has been lost to follow-up study. Four out of 5 who survived are doing well in a stabilized state or improvement on a home regimen. No recurrence of hernia has been observed during a follow-up period of five months to five years. One patient (Case 11) is presently being treated at a tuberculosis sanatorium for the peritoneal tuberculosis discovered at the time of herniorrhaphy.

Discussion

Early repair of uncomplicated hernia is usually considered good surgical practice. Sometimes, patients require repair at once because of incarceration or strangulation or in cirrhosis owing to spontaneous leakage of ascitic fluid. Moreover, the high rate of hernia found by Chapman et al.[1] and by Henriksson[2] increases the number of complications to be expected in patients with cirrhosis.

A chronic debilitating disease such as cirrhosis, however, might well compromise the prospects for a good surgical repair. The characteristically poor nutritional state of these patients might be expected to be accompanied with delayed or poor wound healing. Anemia and ascites might also contribute to a poor outcome.

The results presented in this report, although the series is small, indicate that hernia repair can be undertaken with the expectation of good wound healing. All wounds (except 1 in which the small bowel was inadvertently entered) healed by primary intention in spite of poor (although often improving) nutrition in most cases. Scrupulous treatment for as long as possible before operation was undertaken and careful preoperative preparation, anesthesia and postoperative management probably contributed a good deal to these results. The importance of good food intake, first emphasized by the classic work of Patek et al.,[10] the ability to control the formation of ascites and the improved knowledge of factors precipitating hepatic coma were applied to the care of the patients reported in this series and are discussed briefly in the paragraphs to follow.

Patients with cirrhosis of the liver are almost always able to maintain positive nitrogen balance when a diet adequate in protein is provided, although return to a normal nutritional state may be slow.[11] Our custom has been to provide approximately 1 gm. of protein per kilogram of body weight — more when deemed necessary and less or none if food protein is related to early signs of hepatic coma, as it is in a few susceptible patients.[12] A well rounded diet of good foods without restriction of fat has been used to provide adequate calories, vitamins and other nutrients.

The formation of ascites and edema by patients with chronic liver disease can be controlled by rigid restriction of sodium intake to approximately 200 mg. daily.[8,9] This will prevent further accumulation of ascitic and edema fluid in almost every patient. A few require some control of fluid intake in addition to sodium restriction. Mercurial diuretics sometimes induce a moderate diuresis. Occasionally, the combination of rigid sodium restriction, mercurial diuresis and the dehydrating effects of paracentesis may produce hyponatremia and the sodium-depletion syndrome. Rigid sodium restriction alone, however, is well tolerated by these patients and may occasionally lead to prompt diuresis with loss of ascites and edema, but for the majority it must be continued for weeks, months or even a year or so. Eventually, if continued long enough, these patients will lose ascites and gain flesh (Fig. 1). As diuresis proceeds, whether it is prompt or delayed, the serum sodium concentration when low, which it often is in chronic cirrhosis with ascites, usually rises to or toward normal. All the patients in this series had been provided with sodium-restricted diets before operation for varying periods, many already demonstrating some improvement in nutritional status, rise in serum albumin concentration and decrease in ascites and edema. They were thus improved nutritionally, from the standpoint of liver function and ascites, before operation was undertaken.

Because of the possible danger of inducing bleeding from esophageal varices or acute pulmonary edema, albumin was not given to these patients to correct hypoalbuminemia before surgery or to induce diuresis, which it will do in a small proportion of patients with ascites and edema.[13] Small quantities of albumin (approximately 25 gm.) given daily for a few days may be harmless; however, the rise in serum albumin

concentration is temporary, and albumin so administered merely enters the metabolic pool since it is broken down and adds no more to the patient's nutrition than an equal amount of protein given by mouth.[13,14]

Another complication of cirrhosis that influences preoperative medication and the postoperative course is the susceptibility of a few patients to the development of hepatic coma, the most common cause of death after operation on patients with severe liver disease. Recent investigations have pointed out that not only may surgical procedures and paracentesis induce hepatic coma in susceptible patients but also the injudicious use of sedatives and analgesics, acute loss of blood and severe infections may be implicated.[15] None of the patients in this series manifested this usually fatal condition, although one had evidence of impending hepatic coma, represented by mental confusion and the characteristic "flapping" tremor, on admission to the hospital, but it had disappeared three or four weeks before operation. A few hours postoperatively the syndrome again appeared and lasted for three or four days but did not progress into deep coma. Ammonium chloride has been shown to precipitate hepatic coma in susceptible patients[12]; hence it should be administered as a diuretic with the greatest caution, and its administration should be discontinued at the earliest sign of impending coma.

Because the long-chain, shorter-acting barbiturates are excreted to a large extent by the liver (for example, pentobarbital), phenobarbital and especially barbital should be used in their place, but still with caution.[16,17]

Of all the hypnotics and sedatives, morphine and its derivatives are most clearly related to the genesis of hepatic coma in susceptible patients.[18,19] It is assumed that morphine is metabolized largely by the liver. At any rate, clinically its administration to patients with severe liver disease is often associated with the subsequent development of hepatic coma. In our experience meperidine (Demerol), although not free from blame,[20] is better tolerated than morphine, and hence this drug was chosen usually for preoperative sedation as well as for postoperative control of pain. Demerol also has the advantage of greater spasmolytic action and less respiratory depression than morphine.

When endotracheal anesthesia was used, Pentothal Sodium was administered for induction, since this drug presumably is not detoxified by the liver and does not have a prolonged action in patients with severe liver disease.[16,21] Spinal anesthesia was carried out with utmost care to avoid unnecessary hypotension, which compromises the hepatic circulation. Cyclopropane was considered to be the safest inhalation anesthetic, chiefly from the work of Raginsky and Bourne[22] and Engstrand and Friberg.[23] In laboratory animals they found it to have little effect upon normal liver cells. Nitrous oxide was used in 1 patient without apparent harmful effect. Cyclopropane seems to be the better choice.

Local anesthesia was used in 2 of our cases and was well tolerated.* No difficulty was encountered in our patients, nor are there other reports in the literature of difficulties in its use in patients with severe liver disease.

Postoperative care differed little from that before the operation. If absolutely necessary for rapidly reaccumulating ascites, paracentesis was done, but, as noted above, removal of small quantities of fluid at one time would be better tolerated than a large amount. The postoperative course, except for the bleeding mentioned above that was followed by a wound infection, the wound subsequently healing well, was largely uneventful.

A final remark concerns the observation that unexplained hernia may point to a diagnosis of cirrhosis, described well in the old adage, "If an umbilical hernia develops not as a congenital defect or an anomaly, one should suspect either cirrhosis of the liver or carcinomatosis."[26] Occasionally, the surgeon is surprised to find a considerable amount of ascites upon entering the peritoneal cavity for repair of what was thought to be an uncomplicated hernia of the umbilical or inguinal region. Hernia as a presenting complaint in patients with cirrhosis of the liver and ascites is also occasionally observed. Altschule[27] has described 7 patients who presented themselves either with inguinal pain, incarceration or for routine herniorrhaphy in whom cirrhosis with ascites was found unexpectedly. There were 2 cases in the series of Chapman et al.[1] in which herniorrhaphy led to the diagnosis of cirrhosis.

Summary and Conclusions

Herniorrhaphy for patients with severe cirrhosis of the liver with ascites must be undertaken with caution, but is not as hazardous a procedure as might be anticipated. With scrupulous treatment and careful surgical technic a satisfactory result was finally achieved in 16 operations on 11 patients, although many patients had improved in nutritional status and lost some ascites before operation.

Healing of wounds by primary intention occurred in 15 of the 16 operations in spite of undernutrition and chronic liver disease with ascites and hypoalbuminemia.

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*Although procaine has been found to be hydrolyzed in the plasma,[24,25] contrary to the previous belief that it was detoxicated in the liver, it is recommended that care be taken to control the rate of absorption by the addition of epinephrine and not to exceed a total dose of 1.0 to 1.2 gm.

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THE COMMUNITY BLOOD PROGRAM*

DONALD E. BROWN, M.D.†

HACKENSACK, NEW JERSEY

THE usual community blood program consists of three major components: the hospital blood bank; the community blood bank; and walking donors. If the program is to function smoothly and efficiently, the responsibilities and limitations of each component must be clearly delineated. Failure to do so results in friction, and administrative friction, like its mechanical counterpart, produces dissipation of energy and varying degrees of heat.

A blood bank, as defined by the American Association of Blood Banks, is "a medical facility designed, equipped, and staffed to procure, draw, process, store, and distribute human whole blood or its derivatives." There may be some disagreement with this definition, but it is the general consensus that a true blood bank should be able to function as a complete unit without relying on other institutions to handle one or more of the services listed. A hospital blood bank is a blood bank operated by a hospital primarily to serve its own needs and, occasionally, those of other hospitals in the area. A community blood bank is a usually nonprofit facility, locally organized and controlled to serve the needs of the majority or all of the hospitals in a given community.

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†Assistant professor of pathology, Columbia University College of Physicians and Surgeons, New York City; director of laboratories, Hackensack Hospital; formerly, assistant in pathology, Harvard Medical School, member, Supervisory Committee on Blood Banks, Massachusetts Medical Society, and pathologist, Beverly Hospital, Beverly, Massachusetts.

HOSPITAL BLOOD BANK

The hospital blood bank is the pivotal point of the community blood program. Its director is legally and morally responsible for the total supply of blood to his institution. In this capacity he is interested in all available sources. He is much less concerned with who gets the credit than with who gets the blood. He offers a twenty-four-hour phlebotomy and processing service that cannot be approached by most community blood banks. Of considerable importance in these uncertain times is the fact that the hospital blood bank constitutes a decentralized focus that may be expanded to meet the needs of disaster or civil defense.

COMMUNITY BLOOD BANK

The community blood bank serves as a central source of supply to several surrounding hospitals. It offers the distinct advantage of being a relatively large organization committed to a single activity. As a result, the operative costs may be considerably lessened by streamlining and bulk purchasing. It is usually equipped with one or more mobile units, which open up sources of blood frequently closed to the hospital blood bank. This is particularly true in industry, where the blood may be collected as an on-the-job operation. It serves as an excellent training school for blood-bank technicians and phlebotomists.

Its multiple hospital affiliations allow it to buffer excesses in both supply and demand. The buffering of excessive demand, however, is limited by the number of pints currently on the shelf or available in the refrigerators of affiliating hospitals.

Community blood banks may be sponsored by practically any agency, but in general the two major sponsors are the county or state medical society and the American Red Cross. There has been a distressing tendency on the part of some community blood banks to make unrealistic commitments that cannot be fulfilled and to adopt a somewhat cavalier attitude toward hospital blood banks. Conversely, some hospital blood banks have, for reasons of economic or administrative superiority, obstructed the development of community blood banks. This has led to ill will, unfavorable publicity and an air of subdued hostility that operates to the detriment of both agencies involved. It is obvious, therefore, that adequate administrative liaison between the hospital and community blood bank is of the utmost importance to the success of any community blood program.

In the system sponsored by the Red Cross, administrative control is usually exercised by a committee of the state medical society. The effectiveness of this control depends on the make-up of the committee and the backing given it by the medical society. It is imperative that the committee be composed of active blood bankers and that it be given every possible measure of support by the parent society. It should never be forgotten that the Red Cross program is a permissive one, existing only with the approval of the local medical society. Failure to appreciate this fact has sometimes led to unwarranted and even aggressive complacency on the part of the Red Cross and administrative stagnation on the part of the blood-bank supervisory committee.

Although community blood banks sponsored by the county or state medical society should avoid many of the administrative problems of the Red Cross system, this is not always the case. Occasionally, the community blood bank is set up without the co-operation of, or even in opposition to, the directors of the hospital blood bank. Under such circumstances, its administrative policies may not reflect the best interest of the hospital blood bank or even of the program as a whole. In some cases the governing board may offer to accept the directors of hospital blood banks as members of a technical advisory committee, but no blood-bank director should ever allow himself to become incarcerated in this administrative cul-de-sac. Hospital blood banks should be well represented on the governing boards of their affiliating community blood banks, and such representation should be in the category of a full voting membership.

It is frequently recommended that the hospital blood bank sign a contract with the community blood bank regarding the obligations of each party. These contracts state in essence that the community blood bank will guarantee to fill all or a percentage of the institution's blood needs in return for strict adherence to the bank's policy. All hospital representatives must clearly recognize the implications and potential problems inherent in such agreements. They must be completely satisfied that the contract is realistic and workable. Above all, there must be included some practical approach to the situation that will invariably arise on the day that the operating room has a patient with a rare type of blood who is bleeding to death and the community blood bank cannot supply the blood. A significant number of contracts ignore this issue and make no provision for failure of the community blood bank to meet its obligations.

In spite of the many problems that may exist, adequate liaison, practical experience, abundant good will and an earnest desire to succeed will eventually produce a smooth, efficient two-agency program. The joint activities should be so intimately integrated as to produce a solid front. Nothing is more damaging to a blood program than a divergence of philosophy and dichotomy of recruitment.

The success of a well organized community blood program depends largely upon the co-operation of the residents in the area served. The development of such co-operation is, at least in the beginning, chiefly a matter of education and salesmanship. Because of the relative importance assumed by problems of administration, there is sometimes a tendency to sell the public on the program rather than on the product. If the program is not well integrated, this may result in considerable confusion on the part of the donor regarding his rights and obligations. The sole purpose of a community blood program is to provide blood for the patient who needs it. The agencies involved should be of no immediate concern to the participants and under no circumstance should any intramural differences be allowed to influence donor recruitment.

Donors

Donors are recruited from two main groups: the public as a whole; and the friends and relatives of recipients. The general public donates either as a charitable contribution or as a deposit against future needs by the donor or his immediate family. The extent to which such contributions become an insurance depends upon the nature and scope of the program under consideration. Insurance commitments must be given very careful consideration before being put into operation. The statistics needed to place them on a sound actuarial basis are frequently not available. In addition it must always be kept in mind that blood insurance, in contradistinction to most other types of insurance, is paid not in uniform units such as dollars but in the highly selective units of specific blood groups. Statistical analysis of total units is of little value in determining the possibility

of paying off a large debt in a rare blood group. Donations from the friends and relatives of recipients usually constitute either a deposit against a known future demand or a replacement of blood already given.

Although policies concerning recruitment involve both the hospital and the community blood bank, the mechanics of recruitment may be a function of either or both agencies. Successful donor recruitment is not the prerogative of any given group but a function of the compulsion that leads people to donate. In some programs this takes the form of an economic penalty, and in others it assumes the nature of a moral obligation. Motivation produced by economic penalty is simple, straightforward and highly effective. A charge is made for the blood, and this charge is canceled upon the donation of an appropriate amount within the time specified. Moral obligation, in contradistinction, is a complicated and elusive force. When properly utilized, however, it is even more effective than economic penalty. It is fostered by vigorous publicity, aggressive campaigning and even door-to-door solicitation. Various lay groups may be employed to sponsor donor drives, and the competition that develops among them strengthens the general feeling of obligation and desirability of participation. Such group competition, however, is healthy only when all groups are recruiting for a single program. A community blood program is headed for disaster if it permits splinter recruitment agencies to operate for a select few. If splinter groups exist, they must be brought in under the aegis of the community program. This is not always easy, for suspicion, resentment and intense personal pride must be overcome. The problem of each group is unique and its solution frequently takes time, but the welding together of such groups into a single unit is well worth the effort involved.

With all their difficulties resolved, the hospital and the community blood bank should operate as a smoothly functioning, two-agency unit capable of handling the vast majority of demands. There remains, however, a varying percentage of obligations that the community blood program cannot fulfill without help from another source. This source is the walking donor. It is the walking donor who covers the deficits in the supply of the community blood bank, who fills the large, unscheduled requests, particularly for rare types, who provides fresh blood for patients with thrombocytopenia and hemophilia and who is locally available on short notice in the middle of the night. Prospective donors should be clearly informed of their obligations, typed and catalogued. The file should be kept at some convenient location that has twenty-four-hour coverage. Special attention should be paid to rare groups, and such donors should not be bled except upon demand. The availability of walking donors spells the difference between success and failure in a crisis. Their recruitment should be aggressively pursued by all facilities available.

Standards of Blood Handling

Although acceptable technics of blood handling may vary widely, certain minimum standards should be complied with. These are set forth in the regulations of the National Institutes of Health. Unfortunately, the regulations are enforceable only with interstate shipment of blood, and if a blood bank confines its activities to a single state, it is under no obligation to be licensed by the National Institutes of Health or to comply with their rules. Under such circumstances, minimum standards are frequently set by officials of a hospital or community blood bank. Although this action is commendable, it does not produce uniformity throughout the state or even in the area served by a given community blood bank. This presents a real obstacle to the exchange of blood. No community blood bank should accept responsibility for transferring blood from the refrigerator of one hospital to that of another unless it has complete assurance that the technics used in handling that blood meet the standards of the National Institutes of Health. If the community blood bank holds a license from the Institutes, such an action renders it liable to loss of this license. Standards are sometimes set by a committee of the state medical society. This is more effective in producing state-wide uniformity, but usually falls short of its goal because of failure either to require licensure or to allocate funds for adequate inspection and control.

Organization

The majority of blood banks are organized as charitable institutions. Failure to appreciate the precise meaning of this term has led to untidy thinking, particularly by community blood banks. The original concept of a charitable institution dates back to 1601, when the English Parliament under the reign of Queen Elizabeth enacted the Statute of Charitable Uses. This was replaced in 1888 by a new act, which pertains down to the present. Any purpose is "charitable" that is within the types of benevolences stated in the preamble to this statute. With rapidly changing economic and social environment, the designation of an institution as charitable currently finds its chief significance in the fields of income-tax payment and malpractice litigation. A charitable institution has been defined as follows[1]:

> . . . one which pays no dividends, has no capital stock, seeks no profits, and is supported in part by charitable donations . . . That patients who are able to pay are required to do so does not change the fundamental nature . . . The test of a charitable institution in many jurisdictions is not the extent of the free services rendered, nor whether the patients pay more or less than cost for the services, but whether those who operate it are doing so for private profit, directly or indirectly.

It is, therefore, perfectly patent that the running of a blood bank on sound business principles in no way jeopardizes its standing as a charitable institution. Furthermore, it is obvious that, even in its broadest sense, charity means the provision of services for those who are unable to obtain or procure such services for themselves. It does not mean provision of free services to all irrespective of ability to pay. This is not charity; it is socialism. Augmenting the general belief that a charitable institution cannot be as efficient as a business venture for profit is the curious notion that blood and blood derivatives represent some sort of vital biologic substance that is above economic consideration. The term "blood money" and the concept of Shylock's "pound of flesh" have for so long been used to symbolize a reprehensible trading on the misfortunes of others that even the most astute of businessmen become confused regarding the ethics of blood banking. Although such an attitude is understandable, it does not alter the hard fact that blood banking is a business and must be run as such. Failure to do so results in mounting deficits, loss of personnel, increased appeals for public contributions, loss of public faith and eventually collapse of the program, to the detriment of those who are most needful of such a charity.

Perhaps the most pernicious aspect of this philosophy is the protective mask that it throws over incompetence and inefficiency. A loose concept of charity is conducive to loose cost accounting, unwise investments and improper conservation of resources exemplified by inadequate control of outdating and a failure to utilize outdated blood. Any charitable blood bank must run on a budget sufficiently strict to allow reasonable charges with respect to commercial competitors. Although it is true that charitable blood banks, in contradistinction to commercial blood banks, absorb all uncollectable debts, it should not be overlooked that this figure in a well run hospital does not greatly exceed 20 per cent. Furthermore, a charitable blood bank obtains most of its blood without cost, whereas a commercial blood bank pays the bulk of its donors. When the springs of private charity run dry, the possibility of county or state tax funds always remains as a source of support. If this situation is allowed to develop, the private practice of medicine has lost one more outpost to the inroads of socialized medicine. Whereas profiteering in blood is to be vigorously condemned, sound fiscal policy in blood banking is highly recommended.

Discussion

In conclusion, it might be of some interest to review the operation of a typical well functioning community blood program involving two hospital blood banks and a community blood bank sponsored by the Red Cross. The two Massachusetts hospitals, Beverly and Cable Memorial, are located in the Beverly Red Cross area. In the calendar year 1955 they gave 1109 transfusions and had 198 pints of outdated blood (an outdate rate of 15.3 per cent, which is 2.1 per cent higher than the average for the State as given by Lesses and Banton[2]). A considerable portion of this outdated blood was returned as part of the State plasma-salvage program. From July 1, 1954, to June 30, 1955, 9 bloodmobile visits to the area collected 1013 pints of blood, of which the community blood bank (Dartmouth Street Regional Center) returned 890 pints to the hospitals. The remainder was supplied by walking donors supplemented by 58 pints from adjacent hospitals. These walking donors were obtained by an amalgamation of existing small groups and an active recruitment at the time of each bloodmobile visit. The list now totals some 1500 names. The bloodmobile visits are sponsored by various lay groups in conjunction with the Red Cross, and a concerted effort is made to enroll a large number of new donors each time. The hospital blood banks are stocked by ordering from the community blood bank and supplemented by walking-donor contributions to complete the requirements. With the exception of nights, holidays and Sundays all calling of walking donors and ordering of blood is done by the local Red Cross chapter. A part-time secretary is employed for this purpose. In addition to blood-stocking requirements, the secretary is notified daily by the hospital of the names of those who have received blood and in what amounts. She then calls the nearest of kin and recruits them as walking donors or bloodmobile donors or both. Although no economic compulsion is used, the feeling of moral obligation is so strong that a deliberate failure to replace blood is most unusual. The cost to the Red Cross chapter, including the salary of the part-time secretary, was $2,145.73 for the year under discussion. Although the hospitals charge the usual administration fee, now increased slightly by the subsidy to the Red Cross for processing, no charges have been made for blood per se since the start of the program. No professional donors have been used, and on no occasion have the hospital blood banks been unable to provide the blood at the time needed. In 1 case 17 pints were obtained from walking donors on New Year's Eve and at a time when the regional center was unable to be of any assistance. The calling of walking donors on nights, holidays and week ends is a function of the technician on duty, who uses a special list provided by the Red Cross. The program had a long and painful evolution. In the end, however, it emerged as a highly satisfactory joint endeavor that has become an integral part of the community that it serves. The effort expended has been well repaid.

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ELECTROPHORETIC ANALYSIS OF SERUM PROTEINS IN INFANTS AND CHILDREN*

I. Normal Values from Birth to Adolescence

J. William Oberman, M.D.,† Krikor O. Gregory, B.S.,‡ Frederic G. Burke, M.D.§ Sydney Ross, M.D.,¶ and E. Clarence Rice, M.D.‖

WASHINGTON, D.C.

THE rapid accumulation of pediatric literature describing the occurrence in certain children of the recently recognized clinical entity, congenital agammaglobulinemia (hypogammaglobulinemia),[1-3] has stimulated further research into the changes in the serum-protein fractions produced by other illnesses in patients in the pediatric age group. Before investigation of the alteration of serum-protein patterns in pathologic states in children can be performed, however, it is necessary to establish the normal range of values of the separate protein fractions in young infants and children. The data[4-10] on this subject are sparse, and were compiled mainly in the era before filter-paper electrophoresis; in addition most reports contain too few cases to be statistically significant. The first objective of this study, therefore, became that of determining the normal range of values of each serum-protein fraction in a specified number of apparently well infants and children from birth through infancy and childhood and into early adolescence.

Figure 1 shows the electrophoretic pattern produced by the fractionation of the serum proteins in a normal four-year-old child. At the bottom of the figure a typical paper strip may be observed; at the top is the corresponding pattern produced when this paper strip is analyzed by a densitometer. In the center of the figure are the integration notches, which facilitate the calculation of the total area under each protein fraction. It will be noted that the albumin fraction is represented by a band of the greatest intensity of color and also that the total area under this fraction is by far the largest. Alpha$_1$ globulin may be seen as a just discernible band, the alpha$_2$, beta and gamma globulins each forming a somewhat larger percentage of the total.

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†Instructor in pediatrics, Georgetown University School of Medicine; research fellow, Research Foundation of the Children's Hospital.

‡Chemist, Research Foundation of the Children's Hospital.

§Professor of pediatrics, Georgetown University School of Medicine; assistant attending, Children's Hospital.

¶Assistant clinical professor of pediatrics, Georgetown University School of Medicine; associate attending, Children's Hospital.

‖Associate professor of pediatrics in pathology, Georgetown University School of Medicine; chief pathologist and director of laboratories, Children's Hospital; director of laboratories, Garfield Memorial Hospital.

Materials and Methods

This study includes data on the fractionation of the serum proteins of 159 well infants and children at ages ranging from birth through thirteen years. Included are the results obtained from the cord blood of 26 newborn infants (data on fractionation of the serum proteins of the mothers of these infants just before delivery are also referred to in this study) and on 19 of these infants during the first week of life. The remainder of the material includes data obtained

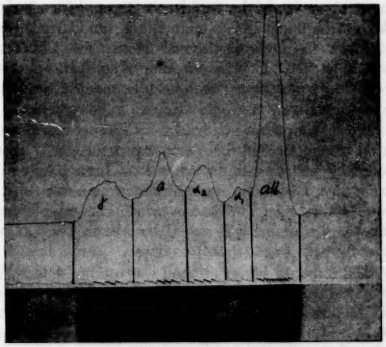

Figure 1. *Electrophoretic Pattern of the Serum Proteins of a Normal Child.*

from other infants and children divided into the following arbitrary age groups: one and two months; three and four months; five and six months; seven through eleven months; one and two years; three through five years; and six through thirteen years. Since values determined in selected infants were found to be comparable before and after meals no attempt was made to ensure that blood was drawn in the fasting state. Any infant or child who had had any evidence of infection, however mild, in the four months before the laboratory analysis of his serum was automatically excluded from the study.

Blood from pregnant mothers at term, newborn infants (cord blood) and infants three to six days old was obtained from inpatients at the Garfield Me-

morial Hospital, Washington, D. C. The remaining infants and young children were seen in the Well Baby Clinics of the Children's Hospital and the Georgetown University Hospital, Department of Pediatrics; values for older children were obtained from preoperative specimens of children admitted to the surgical service of the Children's Hospital for elective herniorrhaphies and circumcisions, and from well children from the Episcopal Home for Children, Washington, D. C. For purposes of comparison, data obtained from 10 normal, healthy medical students and nurses were also included.

Table 1. *Fractionation of Serum Proteins (Comparison of Filter-Paper Electrophoresis and Tiselius Moving-Boundary Method).*

Case No.	Method	Total Protein	Albumin	Alpha1 Globulin	Alpha2 Globulin	Beta Globulin	Gamma Globulin
		gm./100 ml.	%	%	%	%	%
1	Paper electrophoresis	—	62.98	3.37	13.94	15.38	4.33
	Tiselius	6.37	63.50	3.60	13.00	15.40	4.50
2	Paper electrophoresis	6.62	53.04	4.35	11.30	13.04	18.26
	Tiselius	—	54.10	4.10	10.10	12.70	19.00
3	Paper electrophoresis	—	43.60	6.98	16.28	18.60	14.53
	Tiselius	—	43.90	7.80	14.90	18.90	14.50
4	Paper electrophoresis	4.67	54.12	6.20	13.40	10.82	15.46
	Tiselius	—	56.00	4.30	11.50	12.40	15.60
5	Paper electrophoresis	6.80	47.60	6.99	13.97	16.16	15.28
	Tiselius	—	47.30	7.30	13.70	16.20	15.50
6	Paper electrophoresis	5.71	56.67	8.33	16.67	16.67	1.66
	Tiselius	—	56.80	10.00	15.10	17.30	0.70

Blood samples were drawn by venipuncture, and after clot retraction, the serum was immediately separated by centrifugation. When it was not possible to perform total-protein determinations and electrophoretic analyses on the day in which the sample was drawn, the serum was stored by freezing but in no case for any longer than two days.

The standard biuret method was used to determine the total serum protein.[11] The serum sample is treated with biuret reagent, with which the serum proteins form a biuret complex. Total-protein values are calculated from spectrophotometric readings obtained from a Coleman junior spectrophotometer set at a wave length of 540 millimicrons and measured against a reagent blank set at 100 per cent transmission. The concentration of total proteins in the standard is obtained from a pooled sample of human serums and is determined by the Kjeldahl method.

The method used for electrophoretic analysis of the serum proteins follows closely that described by Durrum et al.[12] but with some modification. A strip of Whatman filter paper, 30 mm. wide, is saturated with 0.075-ionic-strength veronal buffer at pH 8.6 and placed in a Spinco Model R cell. An electric current is sent through this system for half an hour so that the strip can become saturated by capillarity and the system put in equilibrium. At the end of this period, 0.01 ml. of fresh, nonhemolyzed serum is applied to the apex of the paper strip. A current of 12 ma. and 78-100 volts is then applied for seventeen hours. This causes the negatively or positively charged protein particles to migrate toward the opposite pole. Since each protein fraction has a different mobility the serum proteins separate into well defined bands. The strip is dried at 110 to 120°C. for thirty minutes and stained overnight in Spinco dye B-1. It is then rinsed three times in 2.5 per cent acetic acid for ten minutes each time and finally dipped for five minutes in a solution of 2 per cent sodium acetate in 10 per cent acetic acid. After this procedure the strip is blotted dry and further dried for half an hour at 100°C. The intensity of color of each of the bands is a gauge of the concentration of each protein fraction. The paper strip is then placed in a Spinco Analytrol densitometer, which converts the colored bands to graphic form. The relative percentage of total area contained under each component is calculated, and values are converted to a percentage of the whole. Duplicate graphs are made, and the percentages averaged to give as reliable a final value as possible.

Absolute values for each serum-protein fraction are obtained from multiplication of each total-protein value by the calculated percentages of each fraction.

A comparison of results of simultaneous fractionation of selected serum specimens by the electrophoretic method and the classic Tiselius moving-boundary method is presented in Table 1. It will be noted that values compare closely. Case 6, with proved congenital hypogammaglobulinemia, had been receiving prophylactic gamma globulin.

Results

Values for the total serum proteins as well as the percentages of each specific fraction as calculated from data obtained by filter-paper electrophoresis are presented in Table 2. Results for each age are expressed as the mean plus or minus the standard error of the mean, the observed range, and plus or minus 1.96 standard deviations. The last calculation rep-

resents all expected values falling between the 2.5 and 97.5 percentiles (95 per cent of the total population at that age). It will be noted that the observed range of values and the calculated value of ± 1.96 standard deviations compare closely in most cases. Absolute values for the serum-protein fractions are presented in Table 3. The mean values of the total serum protein and each component presented in Tables 2 and 3 are plotted against age and displayed graphically in Figures 2 to 5.

Total Protein

Mean values for total serum protein were significantly lower in the cord bloods of newborn infants than their mothers at term (Table 2 and Fig. 2). When individual pairs were investigated, maternal values were higher in 15 and newborn values in 6 pairs, and values were approximately equal in 3 pairs. This lower total protein in the newborn infant appears to be a reflection of a lower globulin fraction since the mean value for serum albumin is much higher in the newborn infant than in the mother at term (Table 3).

Metcoff and Stare[13] report that the total proteins rise slowly after birth, adult levels being reached by fifteen to eighteen months of age. In our series, mean values for children of three or four months of age or older fall within the observed adult range. The *mean* adult level is reached in the group from one to two years of age and is actually surpassed in the group from six to thirteen years old, apparently because of a higher albumin fraction (Table 3).

Serum Albumin and Total Serum Globulin

Mean absolute values for serum albumin (Table 3) are significantly lower in mothers at term and their newborn infants than in normal adults. As previously suggested by Moore, Du Pan and Buxton,[4] levels of serum albumin tend to be higher in infants than in their mothers at term. These findings appear to be in disagreement with those of Orlandini and his co-workers,[14] who reported no significant differences in maternal and cord blood.

Mean values for serum albumin in children do not significantly differ from the adult after the age of three months but may fall within the observed adult range at any age. The mean level of serum albumin is somewhat greater in the group from six to thirteen years old than in adults, giving rise to the greater values for total protein in these children mentioned above. Although this phenomenon may well be a statistical artifact resulting from the small number of determinations in this series, it is interesting that it has been previously documented by Metcoff and Stare.[13] Total globulin levels in the two groups are quite comparable.

Mean absolute values for serum albumin observed in this series reach adult levels at a somewhat earlier time than that reported by Trevorrow et al.,[15] who found that adult levels are reached sometime between the ages of six months and one year. These authors report the mean adult level of albumin as 4.70 ± 0.32 gm. per 100 ml. This value, as well as that reported by Metcoff and Stare,[13] is considerably higher than that found in our series but undoubtedly reflects the more complete fractionation of serum proteins by electrophoretic means than with the older "salting-out" methods; with these methods, a certain percentage of the alpha and beta globulins precipitates out with the albumin fraction. Albumin-globulin ratios consequently have been found to be 30 per cent lower when protein fractionation is performed by electrophoresis.[13]

Absolute values for serum albumin observed in this series are somewhat lower than values obtained by classic Tiselius electrophoresis and previously reported by Knapp and Routh.[9]

When expressed as percentage of the total protein (Table 2 and Fig. 5), mean values for serum albumin are fairly constant (50 to 60 per cent) for all age groups with the exception of mothers at term, who have a significantly lower level. Highest mean values occur from one to six months of age and probably reflect a compensatory rise in albumin percentage to offset the fall of gamma globulin since the alpha and beta globulins are little altered during this period.

Mean absolute values for total globulin (Table 3 and Fig. 3) are much less in the newborn infant than in the mother at term (in this series, specifically higher in the mother in 22 individual pairs and higher in the newborn infant in only 2 individual pairs), confirming the recent work of Orlandini and his co-workers.[14] The level of total serum globulin remains stable during the first week of life and then falls steadily to reach lowest values at three to four months of age (reflecting the fall of the gamma fraction during this time), after which it slowly begins to rise (Table 3 and Fig. 3) until the period from seven to eleven months, when the mean values for children do not significantly differ from the adult means. A fairly abrupt rise of absolute amounts of both total serum globulin and its gamma fraction occurring at three to five years of age probably reflects the increasing incidence of infection in children of preschool age.

As would be expected, absolute values for total serum globulin and gamma globulin in this series are higher than those of other authors,[13-15] all of whom used "salting-out" methods. For the same reason, adult levels of electrophoretically determined total serum globulin are reached much earlier (seven to eleven months) than when determined by the older chemical method (four years).[15]

Alpha and Beta Globulins

Percentage values for both $alpha_1$ and $alpha_2$

globulins (Table 2 and Fig. 4) are somewhat higher in mothers at term than in their newborn infants. Although the percentage of alpha$_1$ globulin continues to fall slightly until three to four months of age, after the first week of life mean levels of this substance remain fairly constant (4 to 6 per cent) through all ages. Lowest mean values for alpha$_2$ globulin are reached during the first week of life, after which there is a rise to a relatively stable mean value of 11 to 14 per cent throughout childhood. The observed ranges for alpha$_2$ globulin are somewhat greater than those of alpha$_1$ globulin. Mean values for the alpha globulins reach the highest level in the group from seven to eleven months of age, after which there is a tendency to lower values with increasing age, a phenomenon previously noted by Knapp and Routh.[9]

In the observed presence of stable serum-albumin levels during the first week of life coupled with falling gamma-globulin levels, a compensatory rise of the alpha and beta globulins during this period, as recently predicted by Orlandini and his associates[14] and previously reported by Moore, Du Pan and Buxton,[4] would be expected. In this series a compensatory rise was indeed observed to occur but was confined to the beta fraction, which rose sharply during the week after birth.

The mean percentage of beta globulin (Table 2 and Fig. 4) in mothers at term is significantly higher than that in their newborn infants. After the previously noted steep rise occurring in the first week of life (partially explained by several extremely high values in individual week-old infants), the mean percentage of beta globulin remains fairly constant (13 to 16.5 per cent) throughout childhood. The observed ranges of values for the beta-globulin fraction, however, are considerably greater than those for any of the other globulins.

TABLE 2. *Total Serum Proteins and Percentage Components for Various Age Groups As Analyzed by Paper Electrophoresis.*

Age Group	No. of Cases	Total Protein		Albumin		Alpha$_1$ Globulin	
		Mean ± Standard Error	Mean ± 1.96 Standard Deviations†	Mean ± Standard Error	Mean ± 1.96 Standard Deviations†	Mean ± Standard Error	Mean ± 1.96 Standard Deviations†
		%	%	%	%	%	%
Mothers at term	26	6.52±0.116 (4.69-7.93)*	5.32-7.72	39.64±1.096 (25.27-52.26)*	28.69-50.59	7.30±0.302 (4.03-9.95)*	4.28-10.32
Babies at birth (cord blood)	26	6.16±0.080 (5.32-6.98)*	5.36-6.96	50.27±1.636 (33.33-64.08)*	34.23-66.30	6.42±0.330 (4.00-10.66)*	3.19-9.66
1 wk. (3-6 days)	19	6.25±0.101 (5.44-6.86)*	5.39-7.12	49.45±1.418 (34.35-57.20)*	37.33-61.57	5.61±0.273 (3.04-8.30)*	3.28-7.93
1 & 2 mo.	13	6.00±0.170 (4.67-6.87)*	4.80-7.20	56.56±1.693 (49.40-66.49)*	44.60-68.52	5.23±0.289 (3.67-7.06)*	3.19-7.28
3 & 4 mo.	13	6.31±0.104 (5.74-6.87)*	5.57-7.05	59.61±1.860 (47.06-67.86)*	46.47-72.76	4.27±0.256 (2.75-5.88)	2.46-6.08
5 & 6 mo.	11	6.31±0.131 (5.72-7.10)*	5.46-7.16	54.62±2.414 (43.85-69.57)*	38.93-70.32	4.84±0.232 (3.80-5.97)*	3.33-6.35
7 through 11 mo.	15	6.68±0.114 (6.07-7.77)*	5.82-7.55	51.90±1.246 (43.98-61.24)*	42.44-61.36	5.66±0.272 (3.45-7.39)*	3.60-7.72
1 & 2 yr.	20	6.92±0.125 (6.43-7.70)*	5.83-8.02	54.69±1.663 (42.46-68.92)*	40.11-69.27	4.93±0.210 (2.78-6.75)	3.09-6.78
3 through 5 yr.	18	7.11±0.083 (6.43-7.70)*	6.40-7.82	50.82±1.207 (41.46-62.30)*	40.78-60.85	5.07±0.272 (2.77-6.74)	2.81-7.33
6 through 13 yr.	24	7.35±0.090 (6.74-8.19)*	6.48-8.21	54.90±0.972 (45.96-65.25)*	45.57-64.23	4.74±0.238 (2.32-6.88)*	2.46-7.03
Adults	10	6.92±0.145 (6.19-7.47)*	6.02-7.82	52.28±1.186 (46.32-58.05)*	44.92-59.63	4.37±0.271 (3.01-5.90)*	2.69-6.05

*Observed range.
†Represents calculated values occurring between 2½ & 97½ percentiles.

Absolute values for the alpha and beta globulins are presented in Table 3. The changes in the mean values for each age group confirm the observations made in the previous discussion of the changes in mean percentage values.

Gamma Globulin

Mean absolute values for serum gamma globulin (Table 3 and Fig. 3) are not significantly higher in the newborn infant than the mother at term, and the mean levels of both do not differ significantly from those of normal adults. These findings confirm those of Orlandini and his co-workers[14] and are in disagreement with the findings of Moore, Du Pan and Buxton[4] and Wiener, Berger and Lenke.[5] In our series individual maternal-newborn pairings revealed higher maternal values in 10 pairs, higher newborn values in 8 pairs and insignificant differences in 6 pairs.

In this series the level of serum gamma globulin is observed to fall steadily to reach lowest levels in the period from three to four months of age, confirming the observations of previous authors.[4,5,10] Wiener, Berger and Lenke[5] believe that practically all the gamma globulin fraction of newborn serum is derived from placental transfer in a manner analogous to the univalent antibodies. They postulate that the newborn infant is unable to form significant amounts of gamma globulin before the age of three months, after which the level of this substance slowly rises. Some indigenous formation of gamma globulin is thought to occur during the first three months of life, however, since the univalent-antibody level falls somewhat faster than the gamma-globulin level.

In our series, mean absolute levels of serum gamma globulin during the first two years of life as calculated from electrophoretic analysis of the serum proteins are significantly higher than those obtained by the precipitation method and recently reported by Orlandini and his co-workers.[14] These authors report a rapid fall of gamma globulin to a third the normal newborn level by the age of one month, with no further decrease during the second and third months of life, and a gradual rise thereafter. We are unable to confirm these findings, agreeing, instead, with Moore, Du Pan and Buxton[4] and Wiener, Berger and Lenke[5] that the fall is much more gradual. Mean values for serum gamma globulin as well as the observed range of values for each month of life from birth through six months of age are collected in Table 4. The number of cases is admittedly small; nevertheless, the gradual trend to lowest levels at three months of age is readily seen.

After the low level of gamma globulin at three to four months of age there is a slow increase until the age of three to five years, when the mean values do not significantly differ from the adult mean. Mean values for children, however, fall within the observed adult range from seven to eleven months of age on. The greatest increment in the amount of gamma globulin appears to occur in the group from three to five years of age.

A study was made of the effect of stimulation with diphtheria-tetanus-pertussis antigen on the level of gamma globulin during the early months of life. Gamma-globulin levels in 18 infants between the ages of three and six months, all of whom had been perfectly well up until that time, were compared. Ten of these infants had received one or more injections of the antigen, and 8 had never received any of this substance. The mean gamma-globulin level for the immunized infants was 0.548 gm. (range 0.37-0.69 gm.), and that for the nonimmunized infants 0.570 gm. (range 0.03-0.99 gm.) per 100 ml. The difference is not statistically significant, and it will be noted that both highest and lowest values occurred in the nonimmunized group.

TABLE 2 *(Concluded).*

AGE GROUP	ALPHA$_2$ GLOBULIN		BETA GLOBULIN		GAMMA GLOBULIN	
	MEAN ± STANDARD ERROR	MEAN ±1.96 STANDARD DEVIATIONS	MEAN ± STANDARD ERROR	MEAN ± 1.96 STANDARD DEVIATIONS	MEAN ± STANDARD ERROR	MEAN ± 1.96 STANDARD DEVIATIONS
	%	%	%	%	%	%
Mothers at term	12.89±0.548 (6.59-17.43)*	7.41-18.37	21.55±1.359 (13.33-45.05)*	7.97-35.14	18.64±0.562 (13.95-23.70)*	13.02-24.26
Babies at birth (cord blood)	10.97±0.449 (7.18-15.27)*	6.58-15.36	11.79±0.927 (6.80-25.38)*	2.71-20.88	20.59±0.779 (13.11-26.18)*	12.96-28.22
1 wk. (3-6 days)	9.65±0.409 (5.52-11.94)*	6.16-13.14	16.78±1.786 (8.62-42.73)*	1.52-32.05	18.51±0.893 (13.15-26.18)*	10.88-26.15
1 & 2 mo.	12.15±0.810 (6.87-16.97)*	6.43-17.88	14.38±1.00 (8.76-24.31)*	7.29-21.47	11.68±0.596 (8.46-15.50)*	7.46-15.89
3 & 4 mo.	12.81±0.614 (9.42-15.81)*	8.47-17.14	15.29±1.175 (9.74-25.74)*	6.99-23.60	8.02±0.486 (4.97-11.48)*	4.59-11.46
5 & 6 mo.	13.14±1.416 (6.86-19.63)*	3.93-22.36	16.29±1.160 (10.74-20.59)*	8.74-23.83	11.10±0.768 (7.60-15.22)*	6.11-16.09
7 through 11 mo.	13.85±0.501 (11.25-18.06)*	10.05-17.65	16.08±0.638 (12.32-20.45)*	11.24-20.92	12.57±0.573 (8.43-16.25)*	8.22-16.92
1 & 2 yr.	12.46±0.551 (9.29-18.11)*	7.62-17.29	14.32±0.697 (7.14-19.65)*	8.20-20.43	13.60±0.721 (7.56-19.53)*	7.28-19.91
3 through 5 yr.	12.71±0.606 (8.79-17.43)*	7.67-17.74	15.02±0.671 (9.52-22.44)*	9.44-20.60	16.38±0.703 (10.12-21.42)*	10.54-22.23
6 through 13 yr.	10.97±0.434 (6.95-15.00)*	6.80-15.14	13.07±0.411 (8.65-17.13)*	8.84-17.30	16.31±0.611 (10.58-22.00)*	10.44-21.18
Adults	11.97±0.688 (9.19-15.90)*	7.70-16.23	13.52±0.578 (10.80-16.52)*	9.94-17.10	17.91±1.477 (10.32-26.42)*	8.75-27.07

*Observed range.

Discussion

Electrophoretic analysis of the serum proteins is not new. Tiselius[16] is usually given credit for developing the technics through which such complex substances as the serum protein could be fractionated. Over the years a considerable literature has evolved concerning the changes in the protein of the blood serum (and plasma) that occur in many diseases and pathologic states.[6,17] The bulk, expense and complexity of operation of the Tiselius apparatus has prevented all but a few large laboratories from collecting and publishing data on any significant number of cases. However, since the introduction of the method of analysis by paper electrophoresis,[12] most of the disadvantages inherent in the Tiselius apparatus have been circumvented. Paper electrophoresis, once the initial cost has been defrayed, is an inexpensive and rapid procedure, and results compare closely with those obtained by the older method.

The use of serum for the analysis of blood proteins has certain advantages over the use of plasma. With the latter, there is an additional fibrinogen peak occurring as a sharp spike between the beta and gamma fractions. This area, however, is a favorite site for the occurrence of abnormalities and the presence of the fibrinogen peak tends to obscure these changes. In addition, deviations in the fibrinogen fraction, except for the rare case of afibrinogenemia, are not specific but usually parallel the alterations in the alpha$_1$-globulin fraction.[17]

Lubschez[8] has demonstrated that the presence of minor infection will result in changes in all serum-protein fractions except the beta globulin. Such changes are most prominent in the first month after the infection (with alterations approaching the magnitude of one standard deviation) but can still be noted to some degree up to four months after the infection. Any interpretation of the results of electrophoretic analysis of the serum proteins must there-

Table 3. *Absolute Values for Serum-Protein Fractions.*

Age Group	No. of Cases	Serum Albumin	Total Serum Globulin	Alpha$_1$ Globulin	Alpha$_2$ Globulin	Beta Globulin	Gamma Globulin
		mean	mean	mean	mean	mean	mean
		gm./100 ml.	*gm./100 ml.*	*gm./100 ml.*	*gm./100 ml.*	*gm./100 ml.*	*gm./100 ml.*
Mothers at term	26	2.58 (1.65-3.39)*	3.93 (3.04-5.62)*	0.47 (0.29-0.65)*	0.83 (0.48-1.12)*	1.42 (0.90-3.26)*	1.21 (0.81-1.58)*
Newborn infants (cord blood)	26	3.09 (2.06-3.95)*	3.08 (1.91-4.28)*	0.40 (0.23-0.68)*	0.68 (0.38-0.90)*	0.73 (0.38-1.63)*	1.27 (0.82-1.67)*
1 wk. (3-6 days)	19	3.08 (2.27-3.76)*	3.17 (2.43-4.35)*	0.35 (0.20-0.51)*	0.60 (0.36-0.78)*	1.06 (0.52-2.83)*	1.15 (0.84-1.54)*
1 & 2 mo.	13	3.40 (2.76-4.52)*	2.60 (1.80-3.34)*	0.31 (0.24-0.39)*	0.73 (0.44-1.15)*	0.86 (0.55-1.48)*	0.70 (0.44-0.94)*
3 & 4 mo.	13	3.76 (3.09-4.42)*	2.55 (1.95-3.63)*	0.27 (0.17-0.37)*	0.81 (0.57-1.08)*	0.97 (0.59-1.76)*	0.50 (0.30-0.67)*
5 & 6 mo.	11	3.44 (2.82-4.56)*	2.87 (2.00-3.71)*	0.30 (0.23-0.38)*	0.84 (0.41-1.33)*	1.02 (0.68-1.33)*	0.70 (0.50-0.99)*
7 through 11 mo.	15	3.46 (2.72-4.26)*	3.20 (2.64-3.88)*	0.38 (0.23-0.50)*	0.92 (0.75-1.13)*	1.07 (0.84-1.29)*	0.84 (0.54-1.03)*
1 & 2 yr.	20	3.77 (2.91-4.85)*	3.15 (1.96-3.95)*	0.34 (0.17-0.48)*	0.86 (0.58-1.33)*	0.99 (0.54-1.35)*	0.95 (0.49-1.41)*
3 through 5 yr.	18	3.60 (3.10-4.51)*	3.48 (2.77-4.37)*	0.35 (0.20-0.49)*	0.91 (0.59-1.30)*	1.07 (0.70-1.61)*	1.16 (0.67-1.56)*
6 through 13 yr.	24	4.03 (3.45-4.98)*	3.32 (2.38-4.39)*	0.35 (0.16-0.53)*	0.80 (0.48-1.06)*	0.96 (0.59-1.34)*	1.20 (0.75-1.68)*
Adults	10	3.63 (2.87-4.14)*	3.29 (2.93-3.48)*	0.29 (0.19-0.36)*	0.83 (0.64-1.04)*	0.94 (0.71-1.14)*	1.23 (0.76-1.70)*

*Observed range.

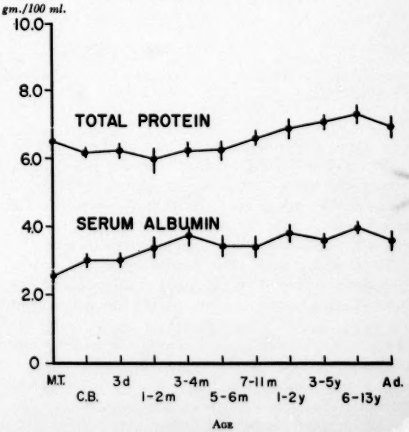

Figure 2. *Mean Values (and 95 per Cent Confidence Limits of the Mean) for Total Protein and Serum Albumin by Age.*

fore take the role of preceding disease into account.

Summary and Conclusions

In an attempt to establish the range of normal values of specific components of the blood serum proteins, fractionation by paper electrophoresis was performed on blood samples from 159 "well" infants and children ranging in age from birth to thirteen years. Only children who had been totally free of infection for at least four months before the fractionation were chosen for inclusion in the study.

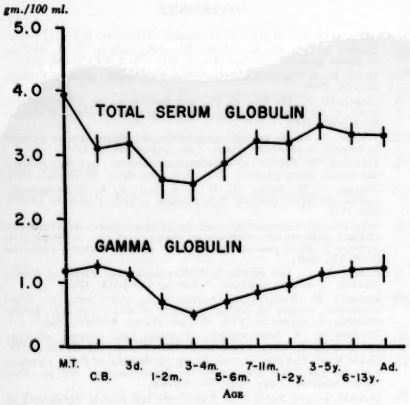

Figure 3. *Mean Values (and 95 per Cent Confidence Limits of the Mean) for Total Serum Globulin and Gamma Globulin by Age.*

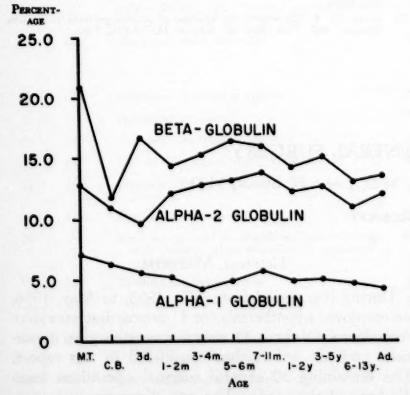

Figure 4. *Mean Percentages for Alpha$_1$, Alpha$_2$ and Beta Globulins by Age.*

Mean values for total serum protein are significantly lower in newborn infants than in their mothers at term. The level of serum proteins rises slowly after birth, mean values for children reaching the adult level by one to two years of age but falling within the adult range as early as three to four months of age. Children six to thirteen years of age have a somewhat higher total protein level than adults.

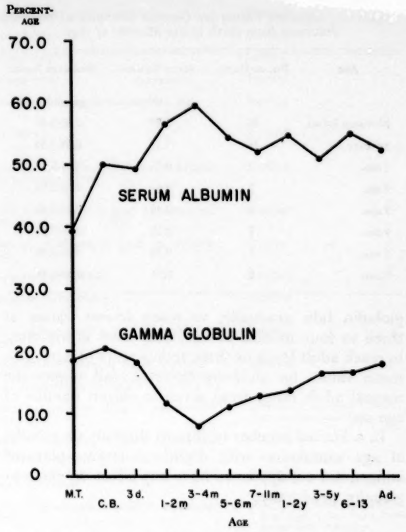

Figure 5. *Mean Percentages for Serum Albumin and Gamma Globulin by Age.*

Mean absolute values for serum albumin are significantly lower in mothers at term than in their newborn infants. The mean level of serum albumin falls within the adult range at any time after birth, the adult mean being approximated at three months of age. Children six to thirteen years of age have a somewhat higher serum albumin level than adults, accounting for the higher total protein levels observed in these children. When expressed in percentage of total protein, mean values for albumin are fairly constant (50 to 60 per cent) at all age groups.

Mean absolute values for total serum globulin are lower in the newborn infant than in the mother at term. After birth the level of serum globulin falls steadily, to reach its lowest value at three to four months of age, after which it rises at a rate to reach adult levels by seven to eleven months of age.

The alpha and beta fractions of the serum globulin are higher in the mother at term than in her newborn infant. After a slight fall in the alpha globulins

and a steep rise in beta globulin occurring during the first week of life, mean percentage values of these substances remain fairly stable throughout life, with a tendency to lower values with increasing age. The range of observed values of beta globulin is somewhat greater than that of the alpha globulins.

Mean values for serum gamma globulin are not significantly different in mothers at term, newborn infants and normal adults. The level of serum gamma globulin falls gradually, to reach lowest values at three to four months of age, and then slowly rises, to reach adult levels by three to five years of age. The mean values for children, however, fall within the normal adult range from seven to eleven months of age on.

TABLE 4. *Absolute Values for Gamma Globulin at Monthly Intervals from Birth to Six Months of Age.*

AGE	NO. OF CASES	MEAN GAMMA GLOBULIN	OBSERVED RANGE
		gm./100 ml.	*gm./100 ml.*
Newborn infant	26	1.27	0.82-1.67
3-6 days	19	1.15	0.84-1.54
1 mo.	7	0.73	0.44-0.94
2 mo.	5	0.67	0.53-0.94
3 mo.	6	0.45	0.30-0.58
4 mo.	7	0.55	0.37-0.67
5 mo.	5	0.70	0.50-0.99
6 mo.	6	0.71	0.50-0.94

In a limited number of infants three to six months of age stimulation with diphtheria-tetanus-pertussis antigen did not appear to have any effect on gamma-globulin production.

We are indebted to Herbert A. Sober, Ph.D., senior scientist, National Cancer Institute, National Institutes of Health, for results of serum-protein electrophoresis performed by Tiselius fractionation, and to Mary M. Wilkinson and Nathan Mantel, of the Biometry and Epidemiology Branch of the National Cancer Institute, National Institutes of Health, for statistical analysis of results.

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HYPOTHERMIA IN GENERAL SURGERY*

B. EISEMAN, M.D.,† J. C. OWENS, M.D.,‡ AND H. SWAN, M.D.§

DENVER, COLORADO

DURING the past three years a voluminous literature has accumulated on the use of hypothermia in prolonging the safe period of circulatory occlusion during cardiac surgery, but little has been written on the use of hypothermia in general surgery. The purpose of this paper is to summarize our experience with the use of hypothermia in general surgery and to give the physiologic rationale for its employment.

*From the Department of Surgery, University of Colorado School of Medicine, and the Veterans Administration Hospital.

†Associate professor of surgery, University of Colorado School of Medicine; chief, Surgical Service, Veterans Administration Hospital.

‡Assistant professor of surgery, University of Colorado School of Medicine.

§Professor of surgery and head, Department of Surgery, University of Colorado School of Medicine.

CLINICAL MATERIAL

During this period from July, 1953, to May, 1956, we employed hypothermia for 41 noncardiac operative procedures. Of these, 11 were for neurosurgical operations and are not further considered in this report. The remaining 30 general surgical operations form the basis of this study. The age, diagnosis, operation and outcome of the procedures are listed in Table 1. Grouping according to types of procedures involved is shown in Table 2. It will be noted that extracardiac vascular procedures (9 cases) and operations on or about the liver (12 cases) form the bulk of this experience.

There were 2 deaths in this group. The first patient was a forty-six-year-old man who had a rupturing eight-year-old man who died six hours after operation from generalized bleeding that followed the resection

TABLE 1. *Data in 30 Cases of Extracardiac Operation in Which Hypothermia Was Employed.**

CASE No.	AGE	PREOPERATIVE DIAGNOSIS	OPERATION	RESULT
	yr.			
1	56	Cirrhosis of liver; esophageal varices.	Portacaval shunt	Survival
2	53	Cirrhosis of liver; esophageal varices.	Portacaval shunt	Survival
3	48	Cirrhosis of liver; esophageal varices.	Portacaval shunt; splenectomy.	Survival
4	26	Cirrhosis of liver; esophageal varices.	Portacaval shunt	Survival
5	9	Cirrhosis of liver; esophageal varices.	Portacaval shunt	Survival
6	60	Cirrhosis of liver; esophageal varices.	Portacaval shunt	Survival
7	52	Laceration of liver, with infection and hemorrhage	Left hepatectomy; cholecystectomy.	Survival
8	5	Biliary cirrhosis; portal hypertension; congestive splenomegaly, with hypersplenism.	Splenectomy	Survival
9	25	Inferior-vena-cava thrombosis; cirrhosis of liver; possible hepatic-vein thrombosis.	Exploration of abdomen; ligation of hepatic artery; biopsy of liver.	Survival
10	60	Aneurysm, abdominal aorta	Excision of aneurysm & graft to abdominal aorta	Survival
11	19	Aneurysm, thoracic aorta	Excision of aneurysm & graft to thoracic aorta	Survival
12	50	Aneurysm, aortic arch	Exploratory thoracotomy	Survival
13	50	Aneurysm, aortic arch, & questionable carcinoma of lung	Exploratory thoracotomy	Survival
14	53	Aneurysm, abdominal aorta	Excision of aneurysm & graft to abdominal aorta	Survival
15	22	Arteriovenous fistula, right common iliac artery & inferior vena cava	Division of arteriovenous fistula between right common iliac artery & inferior vena cava; resuscitation of cardiac standstill.	Survival
16	31	Aneurysm, thoracic aorta	Excision of aneurysm & graft to thoracic aorta	Neurologic changes, lower extremities; survival.
17	16	Aneurysm, thoracic aorta	Excision of aneurysm & graft to thoracic aorta	Survival
18	31	Atherosclerosis, right internal carotid artery	Excision of atherosclerotic internal carotid artery, with graft	Survival
19	68	Aneurysm, abdominal aorta	Excision of aneurysm & graft to abdominal aorta	Patient survived operation but died 6 hr. later from generalized operative bleeding
20	45	Carcinoma of cervix & sigmoid	Exploratory laparotomy; oöphorectomy.	Survival
21	31	Carcinoma of cervix	Wertheim operation	Survival
22	32	Recurrent carcinoma of cervix	Radical hysterectomy; transverse colostomy.	Survival
23	61	Carotid-body tumor, right, postirradiation	Excision of carotid-body tumor	Survival
24	73	Carcinoma, head of pancreas; obstructive jaundice.	Choledochojejunostomy	Survival
25	63	Carcinoma, ampulla of Vater	Modified Whipple procedure	Survival
26	17	Fibrothorax, left; structural scoliosis of thoracic cervical spine, secondary to empyema in childhood.	Plastic reconstruction, left hemithorax; decortication, left lung.	Survival
27	44	Draining pancreatic fistula	Total pancreatectomy	Survival
28	45	Obliterative disease, abdominal aorta	By-pass graft, thoracic aorta & femoral artery	Survival
29	46	Dissecting aneurysm, ascending aorta, & aortic stenosis	None; ventricular fibrillation before operation begun.	Death despite electric and chemical defibrillation & cardiac massage
30	61	Aneurysm of abdominal aorta	Resection of aneurysm	Survival

*Excluding neurosurgical cases.

syphilitic aneurysm of the ascending aorta and aortic stenosis; resistant ventricular fibrillation developed while hypothermia was being induced (31°C.) before operation had begun. The second patient was a sixty- and homograft replacement of an abdominal aneurysm.

Morbidity from hypothermia was limited to 1 patient, who suffered a third-degree burn of the thigh

when rewarming with hot-water bottles was carried out with unwarranted vigor.

The mean age of this group of patients was forty-three, which is much older than that of the usual patient in whom hypothermia is utilized for cardiac procedures. The oldest patient was seventy-three years of age. The temperature employed in the patients in this series was 28-31°C. by rectum, a range similar to that being currently employed in open cardiotomy.

TABLE 2. *Types of Cases in Which Hypothermia Was Employed.*

TYPE OF CASE	NO. OF CASES	OPERATIVE DEATHS	IMMEDIATE POSTOPERATIVE DEATHS
Operation for neoplasm	5	0	0
Thoracic surgery	2	1	0
Vascular surgery	13	0	1
Liver and abdominal disease	10	0	0
Totals	30	1	1

Cooling was done by ice-water immersion in a tub as described elsewhere.[1] Rewarming in the extrathoracic procedures was variously carried out by the use of diathermy coils about the chest, warm-water bottles applied to the extremities or bathtub immersion in warm water after wound closure.[1]

PHYSIOLOGIC RATIONALE FOR USE OF HYPOTHERMIA IN GENERAL SURGERY

Diminution of Tissue Metabolism in Hypothermia

According to the van't Hoff–Arrhenius equation[2] the rate of biologic processes is increased approximately 100 per cent for every 10°C. rise in temperature. Thus, in hypothermia, basal tissue oxygen requirements are lowered.[3] Since the critical time of arterial interruption to an organ or to an extremity depends upon its minimum metabolic tissue needs, hypothermia prolongs the safe period of such arterial occlusion. This is the fundamental characteristic of hypothermia that underlies its use in surgery.

Anesthetic Effect of Cold

Although it has been known for some time that cold will diminish nerve conduction[4] the anesthetic properties of hypothermia were of little clinical importance until generalized body hypothermia was induced in the anesthetized subject. The drowsiness noted in unanesthetized prisoners thrown into ice water by the Germans during World War II was largely a preterminal event.[5] Ice-water immersion of the unanesthetized subject results in a vigorous physiologic response to the overwhelming thermal trauma[6] as the body defenses are mobilized to maintain a homeothermic state. The metabolic response of the anesthetized subject exposed to cold differs in many respects from this pattern. Although there is vigorous peripheral vasoconstriction, some other heat-preserving or heat-producing mechanism such as shivering can be abolished.[7] Adrenocortical response to cooling, which is marked in the unanesthetized subject, is minimized in the anesthetized patient.[1]

Soon after generalized body hypothermia was utilized as an adjunct to general anesthesia, it was discovered that little additional anesthesia was required once body temperature had fallen to 30°C. or below. This is probably due both to the narcotic action of cold and to the decreased rate of detoxification of the anesthetic agent in the cooled subject. Whatever the explanation, the fact remains that less anesthetic agent is required under hypothermic conditions.[8]

Hypotensive Effects of Hypothermia

Generalized body hypothermia is accompanied by hypotension. As body temperature falls the pulse slows, cardiac output is decreased, and arterial pressure diminishes.[9] The true arterial pressure is only accurately determined in the hypothermic state by the utilization of an indwelling arterial needle or catheter. Auscultatory blood-pressure devices such as the commonly employed Riva–Rocci apparatus are grossly inaccurate in hypothermia because of vasoconstriction, diminution of the pulse pressure and the increase in blood viscosity and consequent change in the blood turbulence upon which determination of auscultatory blood pressure depends.[10] It is a common operative experience during hypothermic anesthesia for the anesthesiologist to find the auscultatory blood pressure unobtainable and yet for obvious pressure to be present in the arterial tree at the time of arteriotomy.[8]

The arterial blood pressure commonly falls approximately to 70 systolic, 40 diastolic, in the range of hypothermia (28°-30°C.) usually employed in general surgical procedures. Hypotension induced by hypothermia is in certain respects preferable to that obtained by blood-pressure-reducing drugs such as the autonomic-ganglion-blocking agents, for with hypothermia, tissue needs for oxygenation are simultaneously reduced with blood flow, whereas with ganglion-blocking agents metabolic requirements remain unchanged. That such a metabolic advantage is not an unmixed blessing is evidenced by the tendency to circulatory collapse and diminished cardiac output that may occur upon rewarming.[11]

SPECIFIC APPLICATION OF HYPOTHERMIA TO GENERAL SURGERY

Interruption of Arterial Supply to an Organ or Portion of the Body

Hypothermia diminishes the rate of tissue metabolic demands, thereby prolonging the period of safe arterial occlusion. This fact may be utilized in the field of general surgery when the critical arterial supply to an organ or to a portion of the body, such as the lower extremities, must temporarily be interrupted for arteriotomy, graft replacement of the vessel, transplantation of the organ or extensive surgery in an avascular field.

The more vital the artery requiring interruption, the more valuable the protection of hypothermia. For this reason hypothermia has found its most common use in procedures requiring aortic occlusion.

Crossclamping of the thoracic aorta can be tolerated for relatively short periods before ischemic spinal-cord or kidney damage ensues. Hypothermia will prolong the safe period of such occlusion.[12,13] In the operative resection of most obliterative lesions of the aorta, such as coarctation, hypothermia is usually unnecessary, for abundant collateral vessels exist. In the resection of nonobstructive lesions, such as thoracic aneurysms, hypothermia is routinely employed. We are now aware that factors besides body temperature and total time of aortic occlusion may be of critical importance in avoiding spinal-cord damage, for in resection of the lower thoracic aorta, the vital nutrient artery to the cord arising at the tenth thoracic segment may be sacrificed and ischemic damage to the cord may occasionally result[14] despite the protection of hypothermia.

Early in our experience we employed hypothermia in all resections of the abdominal aorta, but now realize that this is not always necessary. Crossclamping of the normal aorta below the renal vessels is tolerated for periods up to two hours. In atherosclerotic obliterative disease the abundance of enlarged collateral vessels prolongs the safe occlusion time and makes it unnecessary to employ hypothermia. Excision of such an atherosclerotic abdominal aorta should be accomplished with much less than two hours of aortic occlusion. When atherosclerotic plugs extend above the renal vessels they can be removed from the open end of the severed proximal aorta while an assistant temporarily maintains hemostasis by finger compression of the aorta proximal to the celiac and renal vessels.

Hypothermia is sometimes employed in the resection of abdominal aneurysms when the defect extends above the renal arteries, or when prolonged aortic occlusion is anticipated because of extensive involvement of surrounding viscera by the lesion.

Hypothermia has also been utilized for prolonging the safe time of vascular occlusion to an organ or region of the body to attain a completely avascular operative field. In 3 patients hypothermia was employed when prolonged aortic clamping was anticipated during pelvic exenteration through an area of previous irradiation. In 3 other patients hypothermia was employed when pancreatectomy was anticipated through an operative field known to be complicated by numerous vascular adhesions. Bleeding under these circumstances is sometimes further minimized by the marked degree of vasospasm, the increased viscosity of the blood and the degree of hypotension attained.

In 3 cases in which major liver resections were required, prolonged safe occlusion time of the vessels in the porta hepatis was made possible by the use of hypothermia.

Reduced Use of Depressant Anesthetic Agents

In selected situations in which the hepatotoxic effect of anesthetic agents must be minimized, the narcotic and anesthetic action of hypothermia can be utilized, but as with any agent, it should be done only when the risks of its use are outweighed by the benefits to be attained. Such a situation occurs in operations on patients with advanced cirrhosis in which the metabolic insult of prolonged anesthesia threatens to precipitate liver failure.

We have so used hypothermia as an adjunct to anesthesia in 6 cases in which portacaval anastomoses were performed for the control of portal hypertension. Pentothal, muscle relaxants and ether were required only for the fifteen to thirty minutes of induction and intubation and while the patient was being cooled; the remainder of the three or four hours of the procedure was carried out with hypothermia as the major source of anesthesia.

It is difficult to judge the efficacy of this procedure, but patients undergoing portacaval anastomosis under hypothermia seem to have had a more benign postoperative course than might otherwise have been anticipated. Studies of liver function before and after operation support these conclusions. Both experimental[15] and clinical[16] evidence indicates that hypothermia has no hepatotoxic effect and that it has a protective effect on the liver when the arterial supply of this organ must temporarily be interrupted.

Hypothermia might well be considered in the anesthetic management of patients with severe liver disease requiring other types of operation.

Problems Peculiar to Abdominal Surgery

The problems and dangers inherent in the use of hypothermia in cardiac surgery are naturally present in the use of this agent for surgical procedures elsewhere in the body. Ventricular fibrillation of a peculiarly resistant sort[17] is characteristic of the modality under any circumstance. Hyperventilation and the avoidance of hypercapnia minimize this danger,[18] but the surgeon and the anesthesiologist must be alert for signs of its occurrence throughout the period of cooling, during the operation and during the rewarming period. When working in the chest the surgeon has the heart directly in view, and any cardiac irregularity is immediately evident. During laparotomy, on the other hand, the surgeon does not have this advantage, and the anesthesiologist must keep an ever-watchful eye on the cardioscope or the constant-writing electrocardiograph to detect such irregularities at the earliest moment.

It is significant that in this series of general surgical cases with operation under hypothermia, there was only 1 death from cardiac arrythmia. In addition 1 patient entered cardiac arrest on induction, primarily owing to profound circulatory disturbance because of an arteriovenous fistula (Case 15, Table 1).

There are at least two explanations for the lack of this complication in these general surgical procedures. In the first place, temperatures between 28 and 30°C. are employed rather than levels of 25 to 26°C. formerly utilized in many patients undergoing inflow and outflow cardiac occlusion. The lower temperatures, at which cardiac irregularities are more frequent,[19] are thus avoided. Probably of more importance is the fact that, in contrast to the patient undergoing cardiac surgery, the patient undergoing general surgery has no inherent myocardial or valvular disease, and cardiac manipulation is avoided. This experience indicates that cardiac arrythmias are less common and of less significance in the use of hypothermia in general surgery than in cardiac surgery. Nevertheless, the general surgeon no less than the cardiac surgeon employing hypothermia must be prepared to perform a thoracotomy and initiate prompt manual, electric and chemical resuscitative and defibrillatory measures.

Evaluation of blood-volume deficit during laparotomy under hypothermia is both particularly important and difficult to attain. Recently, it has been shown in this laboratory that the hypothermic subject withstands blood loss poorly[20] and that hypovolemia, shock and cardiac failure are apt to occur during the period of rewarming.[21]

These observations emphasize the importance of prompt and accurate blood replacement to the patient undergoing operation under hypothermia. During thoracotomy most of the blood lost from the heart and great vessels is immediately transferred into the suction bottles, where it is easily measured, but in the abdomen such shed blood may be hidden behind viscera or may be absorbed into abdominal pads, where its volume is more difficult to estimate.

The problem is further complicated by the difficulty of properly evaluating the condition of the hypothermic patient during operation, for most of the usual indicators of impending or actual shock are rendered inoperative. The skin is cold and blanched because of intense vasoconstriction of the dermal vessels. The bradycardia, hypotension and diminished respiratory rate incident to hypothermia all complicate the usual criteria for evaluating the compensatory response of the cardiovascular system to oligemia. Further confusion results from the bright-red color of hypothermic blood (and of vascular abdominal viscera) that is due in part to the shift of the hemoglobin dissociation curve with cooling. Thus, the surgeon and anesthesiologist must be prepared to abandon many of the usual signs of hypovolemia during hypothermic anesthesia — a situation that is particularly dangerous during an extensive laparotomy.

Closure of a laparotomy wound after a prolonged operative procedure in the presence of hypotension may well result in large amounts of postoperative intra-abdominal hemorrhage from open vessels that begin to bleed when normal blood pressure is reestablished. Unfortunately, this surgical principle must often be violated when one is closing the abdominal incision of a patient who is hypothermic and therefore hypotensive. In cardiac or thoracic surgery an appreciable amount of body warming can be attained by means of a diathermy coil wrapped around the abdomen, where the large volume of blood in the splanchnic bed is warmed as soon as the surgical need for hypothermia has passed.

In the performance of abdominal procedures under hypothermia we have on occasion placed the diathermy coils around the thorax but have hesitated to have such obstructing paraphernalia overlying the site where an emergency thoracotomy for cardiac fibrillation necessarily would be placed. If massage or defibrillatory procedures are required, the delay in removing the coils might well prove fatal. Although abandonment of warming diathermy coils during abdominal surgery on the hypothermic patient leaves the thorax unencumbered it may be a heavy price to pay, for closure of laparotomy wounds under these conditions is usually performed in the presence of some degree of hypotension.

Certain less-effective warming technics may be utilized to attain normotensive levels at the time of abdominal-wound closure, such as the careful application of warm-water bottles to the extremities when the need for hypothermia has passed. This requires great caution because the skin of the hypothermic patient may burn under conditions that might well be tolerated by the normothermic person. The temperature differential between the hot-water bottle and the sluggish circulation in the hypothermic skin, as well as the intense vasoconstriction of the dermal vessels, probably produces this increased susceptibility to thermal trauma.

No adequate solution to this clinical problem, which is peculiar to the use of hypothermia in abdominal surgery, has yet been found. Possibly, some type of extracorporeal blood-warming device would be worthy of trial.

Future Applications of Hypothermia in General Surgery

The clinical use of hypothermia is but a few years old. As the physiologic properties of this agent are clarified by experimental and clinical experience, new applications are certain to be investigated.[22] Some of these functions are already under study.

Hypothermia and Bacterial Infection

Bacterial growth is markedly diminished by a lowering of environmental temperature. Many pathogenic organisms that multiply at body temperature are almost dormant below 24°C. Since the temperature can be tolerated by the laboratory animal and by man for prolonged periods hypothermia may be of value in arresting certain resistant bacterial infections. The critical fact to be determined is whether the immuno-

logic response to infection by the host will be diminished at the same rate as or at a different rate from change in bacterial growth. If the growth and reaction rates of the two factors parallel each other no host benefit will result: hypothermia will then merely "stop the clock" and the calendar as far as the infection is concerned, with no benefit to the host after rewarming. A number of isolated and largely uncontrolled clinical reports of the use of hypothermia in infection have appeared and suggest that hypothermia may be of therapeutic value.

Preliminary indications in our laboratory suggest that mice with peritonitis due to Type 3 pneumococci kept at body temperatures of 21°C. for twenty-four hours have prolonged survival periods as compared to the normothermic controls, and that such survival is more than can be accounted for by mere inhibition of bacterial growth during the period of cooling.[23]

Summary

Experience in the use of hypothermia in 27 noncardiac general surgical operations is reviewed. The physiologic basis for the use of hypothermia in general and abdominal surgery is summarized.

Hypothermia has been used in general and abdominal surgical operations in which prolonged interruption of the critical arterial supply to an organ or a body area is required; in patients with marked cirrhosis, to minimize the administration of hepatotoxic anesthesia agents; and occasionally as a hypotensive agent, to minimize operative blood loss.

Some of the problems of applying hypothermia to abdominal surgery are described.

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SPECIAL ARTICLE

INSOMNIA

Philip Solomon, M.D.*

BOSTON

INSOMNIA is one of the commonest symptoms encountered by the physician, occurring frequently in patients in all branches of medicine; indeed, it has been experienced at one time or another by practically everyone, sick or well. In this country more than $100,000,000 is spent annually on soporifics. Medical textbooks contain few references to insomnia, and medical students are often given little understanding of the condition.

Insomnia may be defined as the inability either to fall asleep or to maintain sleep adequately. Before its causes and treatment are discussed it may be well to consider what is known clinically about sleep itself.

*Assistant clinical professor of psychiatry, Harvard Medical School; visiting psychiatrist and physician-in-charge, Psychiatric Outpatient Clinic, Boston City Hospital.

Sleep

Since the basic physiology of sleep is unknown, the many theories concerning it will not be gone into here. Instead, the aspects which may be of interest in connection with insomnia will be discussed.

Falling Asleep

When an infant is fed and comfortable, it soon falls asleep. When tensions caused by hunger or discomfort accumulate, it wakes up. The cycle of tension-relief of tension-sleep-tension is of short duration,

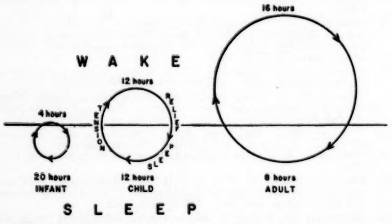

FIGURE 1. *Diagrammatic Representation of the Wake-Sleep Cycle in the Infant, Child and Adult.*

perhaps four hours. As the child grows older and myelinization of the nervous system proceeds further, the instincts develop, and the nature and variety of the tensions become more complicated. Simple food and comfort are not enough for satisfaction. The child has become aware of a fascinating world of objects and people, and he feels many urges toward this world; he must remain awake long enough and must become aggressive enough to satisfy a fair share of these urges before he can relax again and return to sleep. Figure 1 is a diagrammatic representation of the wake-sleep cycle in the infant, child and adult. As the ego grows it can extend further and longer into the complex world of outer reality and conscious wakefulness. Yet it is as though one can endure life's tensions only with intermission — at best, when adult, two thirds of the time; then, one must return for recuperation to a kind of intrauterine state, warm, dark and free of stimulation.

Like a storage battery that needs recharging, the human nervous system requires periodic interludes of sleep to survive. If sleep is interfered with for an extended period, as in ancient Chinese tortures and in some recent experiments, psychosis and death may occur.

Factors conducive to sleep vary with the individual subject. Quiet, darkness, bodily warmth and comfort induce sleep in most people. Although some like a cool room and a breeze, others prefer the windows closed. The popularity of electric double blankets with dual controls bespeaks the variability not uncommonly seen in husbands and wives. Many people obtain a soporific effect from a midnight snack or a hot drink at bedtime; others benefit from walking the dog or taking a hot bath. Some get a lulling reaction from music, and others find nothing so soothing as a serious lecture or a book of required reading.

Motor functions fall asleep before sensory. Inhibitions disappear before impulses, as in alcoholism. Somnolescence is often attended by involuntary muscle jerks, sometimes of the entire body. There also may be peculiar hallucinatory experiences involving disequilibration and strange somatic sensations difficult to describe. Though consciousness, motility and perception usually go together, there are a few conditions in which dissociation occurs. Table 1 describes these in condensed form.

Hypnogogic states are curious experiences in the transitional stage between sleeping and waking. In the mild forms, which most people experience at one time or another, involuntary dreaming seems to occur together with full consciousness. Severe forms have been called "sleep paralysis" and may be associated with panic. As soon as the sleeper can make the slightest motion, the spell is broken.

Catalepsy and cataplexy are pathologic conditions seen in schizophrenia and narcolepsy respectively. Mild forms may occur in normal persons, as witness the phrases "frozen with fear" and "weak from laughter."

TABLE 1. *States of Dissociation between Sleep and Wakefulness.**

STATE	CONSCIOUSNESS	MOTILITY	PERCEPTION
Sleep	0	0	0
Hypnogogic states	+	0	0
Cataplexy & catalepsy	+	0	+
Somnambulism	0	+	0
Partial sleep	−	+	−
Wakefulness	+	+	+

* + = largely present; 0 = largely absent; − = diminished.

Somnambulism is not unusual in normal children, but in adults it indicates psychopathology. Unconscious instinctual impulses are involved that are too strong to be taken care of by ordinary dreaming. Somehow, the motility channels open up.

Partial sleep has been experienced by everyone as drowsiness or being "half-asleep." Its early morning expression is notoriously associated with surliness and bad temper. The ego seems reluctant to get back on the job. At night, drowsiness as a prelude to sleep stimulates imagination and fantasy formation. The ego seems eager to let go of reality. Tired drivers

misinterpret shapes at the side of the road. Writers and creative artists often work late at night to capitalize on their flights of fancy.

Staying Asleep

Depth of sleep can be measured roughly by instruments that record the electric resistance of the skin and by the electroencephalograph. Observations indicate that normal sleep fluctuates markedly in depth during the course of the night. Major body movements usually occur every ten or fifteen minutes, and many sleepers even wake briefly at varying intervals. Surges toward wakefulness often correlate with dream activity.

Dreams represent attempts on the part of the mental apparatus to deal with the upcroppings of the unfinished business of the preceding day. Instinctual drives, unsatisfied and repressed during the day, try to get by the relaxed conscience, but by doing so they threaten to wake the sleeper. If the drives can be dealt with by way of hallucinatory satisfaction, often symbolically and with many disguises, the sleep can go on. Dreams are thus the guardians of sleep. If the drives are too strong, or attendant anxiety too great, the dream fails and sleep is shattered.

Waking

There is great individual variation in the sleep pattern, but usually sleep deepens rapidly in the first hour, remains deep for about four hours and then diminishes in a gradual slope. The last few hours of sleep are light and are enjoyed more for appetite than for hunger. It has been said that the amount of sleep needed is six hours for a man, seven for a woman and eight for a fool. This time-honored edict is probably too strict for the fast pace of modern life, in which more sleep is often required to neutralize the catabolism of the overly filled day.

As anabolism approaches completion, tensions build up again until they tip the balance once more in the direction of waking. The commonest tensions are the predominant and insistent calls of duty — the day's work, habit and the impulses from the hollow organs, bladder and stomach. Wakefulness may occur in an instant or may be more gradual, with functions returning in the reverse order from that of going to sleep. Dreams frequently occur just before waking, and even seemingly long ones may take place in a few seconds.

Causes of Insomnia

The dynamics of insomnia can be clarified by the use of a somewhat whimsical diagram (Fig. 2). The mental apparatus is represented by a swinging bar balanced on a fulcrum, with "fatigue" weighing down one side and "tension" the other. The "world of stimuli" rains down on both sides. During the state of wakefulness (A–A), a reasonable balance is struck between the two sides. As fatigue gradually accumulates, it tilts the bar until one end of it dips down into "sleep" (B–B). But fatigue is soluble in sleep. After a number of hours the load is lightened, and balance is re-established. The swing may go too far if tensions accumulate. Then the other end dips down into "action" (C–C), where tensions rapidly dissolve. Normally, there is a regular rhythmic motion from A–A to B–B and back again, with occasional brief excursions to C–C. The anti-forces on the bar must also be noted. "Rest" tends to neutralize

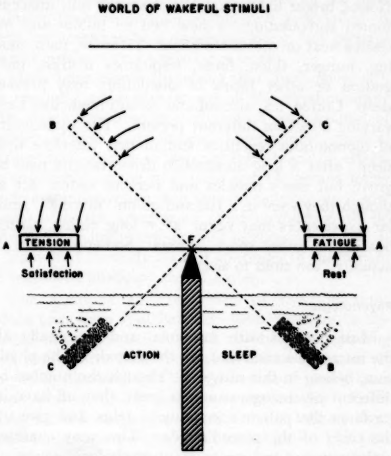

FIGURE 2. *Diagrammatic Representation of the Mental Apparatus, Showing the Balance of Sleep and Wakefulness. The mind is pictured as balanced at the fulcrum* (F). *The world of wakeful stimuli rains down on both sides, to cause both tension and fatigue. When these balance reasonably* (A–A) *wakefulness is present. As fatigue accumulates there is a dip into sleep* (B–B). *After fatigue dissolves in sleep the balance is re-established. If tensions are great and satisfactions little, or if rest is excessive, there is a dip the other way* (C–C) *into action. Solution occurs rapidly here, and balance is again established.*

"fatigue" to some extent, and "satisfaction" lessens "tension."

A glance at the diagram will make it obvious that sleep is interfered with by anything that prevents the bar from rotating in a clockwise direction. There are four logical possibilities (and, of course, combinations of these): insufficient fatigue; excessive rest; excessive tension; and insufficient satisfaction. A fifth possibility, when tensions outweigh satisfactions (as they usually do), is movement of the fulcrum to the right. What this may mean is discussed below.

The first two possibilities are not clinically important in insomnia. Bed patients sometimes do so little and sleep so much during the day that they are unable to sleep as much as usual at night. A rare vacationer may have the same experience. The situation is always obvious.

The second two possibilities cause the bulk of insomnia. Since a truly psychosomatic disorder is involved, it will be useful to group the many etiologic conditions under the headings of "somatic" and "psychologic."

Somatic

Sleep may be interfered with by physical causes either *outside* or *inside* the person. These are all so familiar that they may be dismissed by enumeration. Noises, bright lights, inability to stretch out, unaccustomed surroundings, a new bed or pillow and excessive heat or cold are obvious. Likewise, pain, itching, hunger, thirst, fever, respiratory distress, indigestion or other forms of discomfort may prevent sleep. Coffee, tea, alcohol and certain medicines have varying effect on different persons. The momentum of monotonous repetitive stimuli may interfere with sleep: after a long automobile drive, fatigue may be great, but one's muscles and nervous system act as though they were in a rut and go on "driving"; similar experiences may occur after long riding, skiing, boating or other sport activity. Sometimes, one is actually "too tired to sleep."

Psychologic

Most patients with insomnia, and practically all the intractable cases that are the despair of the physician, belong in this category. Though the number of different psychologic causes is great, they all have in common the patient's inability to relax and give up the cares of the preceding day. One may consider both *conscious* and *unconscious* psychologic causes.

Almost everyone has had the experience of being kept awake by *conscious* emotional tension. The *excitement* of a poker or bridge game may persist for a long time after one has gone to bed. Key hands are played over: wrong finesses or bad bets are reversed, and heated arguments are re-enacted with additions of what one might have said. A thrilling play or motion picture may be run through again and again, to the detriment of sleep. Anticipatory excitement the night before a long-awaited trip may banish sleep. *Anxiety* may be the offender. A doctor worries about a critical patient, a parent over a sick child, a businessman because of a shaky investment, or a student before a final examination. The person with insomnia may worry so about lying awake and its consequences that he may establish a vicious circle. *Anger,* especially if partially or wholly unexpressed, may keep one awake for hours. A wife may lie awake seething besides a snoozing husband, or vice versa. Self-directed aggressive feelings, such as *guilt, shame, remorse or regret,* are fatal to sleep. The human gift of fantasy and imagination is a burden indeed when it results in unending nocturnal brooding on what might-have-been. *Fear* of illness, of pregnancy or of financial ruin has caused many a sleepless night. Sick patients may be kept awake more by fear of the dire consequences of their disease than by the disease itself. Unsatisfied *desire,* such as the tense state of sexual arousal without release, may result in a restless night.

Insomnia produced by any of the conscious somatic causes listed above may be termed *symptomatic insomnia.* In such cases there may be hours of tortured wakefulness before enough fatigue accumulates to swing the balance over into sleep. Even then the sleep may be shallow and uneasy, with impaired refreshing effect. A resurgence of the interrupted emotion may take place early in the morning, producing "matutinal wakefulness," the annoying companion of insomnia.

Patients with the most protracted and unremitting types of insomnia (usually accompanied by a variety of other psychoneurotic symptoms) often honestly deny any anxieties, fears or other intense emotional states. These patients may be said to have *neurotic insomnia.* Here *unconscious* tensions are involved, and prolonged study may be necessary before the offending emotions can be brought to the surface. Any of the conscious emotions mentioned above may exist in a patient's mind without his awareness for months or years in the repressed state. The most frequent repressed emotions that produce insomnia (or any other psychoneurotic symptom) are the sexual and aggressive. An example of each follows:

CASE 1. A 20-year-old single office girl was referred to the psychiatric clinic because of insomnia and other symptoms such as nervousness, lack of energy, poor appetite and headache. In the medical clinic all findings were negative. In psychiatric study she denied any anxieties or frustrations. She was a high-school graduate who had a good job in a large office. She was reasonably attractive and had a fair amount of attention from young men. Only after several visits did it come out that recently a young bachelor uncle had come to live with the family and was occupying the bedroom next to hers. This uncle was something of a rake with the ladies, and he teased the patient constantly about her boy friends and about her rather puritanical attitudes. As she lay awake hour after hour, his insinuating jibes went through her mind. These experiences were so repugnant to her that she repressed them and failed to recount them in the early interviews.

CASE 2. A 23-year-old college senior was referred to the psychiatrist by his family doctor because of insomnia and a variety of other mild symptoms not based on organic disease. The patient talked freely but could recognize no source of anxiety or tension other than his forthcoming final examinations, for which he felt well prepared and which he really did not dread unduly. Later in treatment he reported a dream in which he was made to swab endless decks of a ship, while the captain and first mate stood over him menacingly. The material of the dream clearly came from a Navy R.O.T.C. course, but the meaning became evident only when the patient was asked if the captain and first mate in any way resembled his father and older brother. A flood of feeling then burst forth. The patient after graduation was scheduled to go to business school so that he could enter his father's business. The older brother was already there as the father's right-hand man. The patient had never liked the business but had been compliant. As he talked on, intense feelings of rage, hostility, guilt and self-torture came out. It was now understandable why insomnia developed as graduation from college drew near.

Sleep phobia is a term used for the severest kind of insomnia, in which sleep is not courted actively as

in all the cases referred to above, but is fearfully shunned and avoided as long as possible. Here, one deals more with psychosis than with neurosis, and one may speak of the condition as *psychotic insomnia.* In these patients it is as though the ego perceives itself as so weak or so near the point of shattering that it can be no match for the terrors that lurk in the unconscious. It clings to wakefulness in desperation. These are the patients who may attempt suicide to escape the nameless horrors that seem to threaten them.

Finally, referring again to Figure 2, one may speak of patients in whom the fulcrum of the balancing bar seems to have been shifted to the right. Something of this sort takes place in manic and hypomanic patients. Tensions become inordinately effective, and fatigue carries little weight. When sleep does occur it is brief. If the fulcrum shifts far enough to the right the weight of the bar alone is enough to prevent any dip at all into sleep. These are the patients who wear themselves out with constant activity and the absence of sleep. They sometimes die of exhaustion.

Treatment of Insomnia

The first goal in the treatment of insomnia should be to *eliminate the cause* if possible. In symptomatic insomnia the patient himself is usually aware of the cause and eliminates it as soon as he can. In some cases the physician can be helpful through the administration of specific drugs in their appropriate indications, such as antipyretic, antipertussive and analgesic, increasing the dose as the sleeping hour approaches. In psychologic conditions the physician should encourage an open discussion. When the problems are conscious ones proper action for the elimination of the cause may be self-evident — for example, a patient with insomnia who spends his evenings in spirited gambling should be made to see the advisability of a more sensible regimen. Verbal ventilation alone may be sufficient to relieve a patient who is suffering from remorse. Reassurance may be helpful for the anxious one, and practical advice and encouragement for the fearful.

The physician may attempt to give the emotionally disturbed patient a point of view on sleep. An old German saying is, "The best pillow is a good conscience." But it takes more than a good pillow or a good conscience to produce sleep. One may have a very good conscience indeed and lie awake for hours with unsatisfied tensions and desires left over from the day. One should perhaps add to the German saying: "And the best bed is a day of satisfaction." Each man must find for himself the best balance in the constant fight between the instincts and the conscience. Only then will he arrive at the final axiom: to sleep well, live well.

In neurotic insomnia, more prolonged and specialized psychologic treatment is necessary. Should treatment of this sort be done by psychiatrists only? There are sharp differences of opinion on this question. Some people stress the hazards of psychotherapy in inexperienced hands, pointing out that a little learning is a dangerous thing. Others reply that many of the treatment methods used by physicians involve a certain amount of risk, that every physician utilizes what amounts to psychotherapy anyway in his "bedside manner" and that he would improve his usefulness to patients and minimize the risk if he would increase his skill in the handling of one of his most valuable therapeutic tools — his own personality. A little learning may be a dangerous thing, but perhaps in this instance, no knowledge is worse.

Many have begun to believe that there never will be enough psychiatrists to do all the psychotherapy that should be done in the civilized communities of today. Medical schools and postgraduate medical centers have begun to step up their teaching efforts in psychiatry; many nonpsychiatric physicians today find themselves going into general practice or a specialty with the competence and confidence to do "minor" psychotherapy as well as minor surgery. It is likely that these trends will continue, to the benefit of organized medicine and of society.

The methods and principles of psychotherapy, which have been described elsewhere,[1,2] cannot be discussed in this article. A word may be said regarding the treatment of the 2 cases mentioned above. It might be supposed that the girl in Case 1 would have done well to find herself an active sex life. Some girls, indeed, might have gone about solving their problem in such a way without undue guilt. This particular patient, however, decided to continue postponing sexual relations until after she was married. She did speak to her parents about her young uncle, and his prolonged visit in the home was promptly terminated. For her this was the better solution. She now had a clearer understanding of her sexual status and could accept herself without the previous conflict. Before, she had *had* to be virginal, with the dissenting unconscious part of her expressing itself in insomnia; now she could *choose* to be virginal, with a fuller knowledge of both parts. Treatment had given her a choice. The physician had functioned as a parental figure who permitted her to acknowledge her sexual feelings without condemning her for them.

The young man in Case 2 decided not to break clean from his father and brother as many young men might have done. Instead, he had it out with them and arrived at a compromise. After graduation he would go to law school instead of business school. He would be a professional man and on his own, but since his father's business required a good deal of legal work he and his father and brother would still be associated in a way that would be of benefit to all. Here, the physician functioned both as an instrument to bring to light the patient's hidden aggressions and as a source of moral support to give the patient the

courage to face up to his father and brother, thus expressing some of these aggressions.

The second goal in the treatment of insomnia should be to *counteract the cause* when necessary. Modern sedatives and hypnotics are safe, effective and reasonably inexpensive. Untoward reactions are rare, and aftereffects are minimal. In symptomatic insomnia, which is usually temporary, it is foolish not to avail oneself of chemical help. In Figure 2 sedatives seem to move the fulcrum to the left, thus increasing the weight of fatigue and decreasing the effect of tension. The net effect is to tip the balance toward sleep and keep it there longer.

It is sensible to take a sedative on an overnight train or plane ride, or on the first night or two of a head cold. A sedative may be useful at the end of a long, arduous trip or after any form of prolonged excitement. The wise physician often prescribes a sedative routinely for the patient in the early stages of an acute infection or in any state of acute discomfort. Wakefulness in such conditions serves no useful purpose. The underlying cause is known and temporary, and habituation to sedatives under these conditions need not be feared.

The situation is quite different in neurotic insomnia, in which the cause is psychologic, unconscious and chronic. Here, the use of sedatives is about as sensible as the use of aspirin in the fever of subacute bacterial endocarditis or tetanus. It is true that many sedatives are given to patients with neurotic insomnia and that sometimes improvement seems to result, but the improvement is apt to be partial and short lived. Unless constructive psychotherapy involving recognition, understanding and resolution of the patient's inner conflicts is utilized a state of passive dependency is likely to supervene. The patient's symptoms will recur, and more and different sedatives will be prescribed. What is worse, habituation to these drugs may come about, and the patient's neurotic complaint that his trouble is physical and not psychologic is aided and abetted. Here, one is faced with perhaps the commonest of iatrogenic disorders. In treating neurotic insomnia the physician would do well to keep foremost in his mind the ancient dictum, "Primum non nocere."

Procedures other than pharmacologic for counteracting the various causes of insomnia may be mentioned in passing. Through the ages mankind has devised countless methods for wooing elusive sleep. Magic rites and incantations have vied with philters and potions, charmed amulets with lullabies, and secret walks with perfumed, tepid baths. In modern times one finds conforming mattresses, a variety of "relaxing" appliances, soothing swaying-bed contrivances and special radio and television bedtime programs. But many still pace the floor, smoke endless cigarettes and count myriad flocks of obliging sheep. The pursuit of fugitive sleep for the sufferer from insomnia remains a highly individualized and often baffling enterprise. The search for a remedy is regularly futile when the cause is untreated.

A final word about the treatment of psychotic insomnia. Here, the nonpsychiatric physician can neither eliminate nor counteract the cause. His aim should be to recognize that he is dealing with a psychotic (or, in mild cases, a prepsychotic) condition and to turn the case over as quickly as possible to a psychiatrist. The danger of suicide or death by exhaustion is great, and admission to an institution is usually necessary.

It may be well at this point to review and amplify the diagnostic characteristics of patients with psychotic insomnia. These are persons who shun sleep rather than court it. They are mainly of two sorts: *schizoid,* in which the attitude toward sleep (and their own unconscious) is one of terror and horror, and in which additional symptoms may be present such as, in early cases, feelings of unreality, depersonalization, vague cranial discomfort and ideas of reference and, in later cases, withdrawn or bizarre behavior, mutism, hallucinations and delusions; and *manic,* in which there is no time for or interest in sleep and in which there are the familiar evidences, in early cases, of hyperactivity, overtalkativeness, flight of ideas, elation and defective judgment and, in later cases, wild behavior, push of speech, frenzy and uncontrollability. The complaint of insomnia may be the first clue to the earliest of these cases and perhaps to a way of averting a catastrophe. A young adolescent's continued insomnia may lead one to evaluate more seriously his deteriorating grades in school and his avoidance of his friends, and a shocking suicide may be prevented. A businessman's steadily decreasing need for sleep may throw suspicion on his increasing business and social activities, and a major mental illness may be detected before irretrievable harm is done.

Summary and Conclusions

Insomnia is one of the most frequently seen and least-written-about symptoms in all of medicine. An organized presentation is attempted here, beginning with a discussion of the clinical aspects of sleep. The causes of insomnia are defined as *symptomatic, neurotic,* and *psychotic,* and the characteristics of each are given.

The treatment of insomnia is divided into efforts to remove the cause and methods of counteracting the cause. Sedatives are advocated in symptomatic and psychotherapy in neurotic insomnia.

Patients with psychotic insomnia are dangerous and should be referred to a psychiatrist.

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MEDICAL PROGRESS

SURGERY OF THE BILIARY TRACT (Concluded)*

RICHARD B. CATTELL, M.D.,† AND KENNETH W. WARREN, M.D.‡

BOSTON

STENOSIS OF THE SPHINCTER OF ODDI

The validity of the concept that stenosis of the sphincter of Oddi contributes to biliary-tract symptoms is gradually gaining support. It is being recognized with increasing frequency as a pathologic fact both at the time of initial cholecystectomy and as a cause of continued or recurrent symptoms in some patients after cholecystectomy. Cumulative experiences from several sources indicate that stenosis of the sphincter of Oddi may occur in the absence of any demonstrable common-duct stones and in patients who have not had previous biliary-tract surgery.

The importance of evaluating the status of the patency and caliber of the sphincter of Oddi during gall-bladder surgery, particularly in every case in which valid indications for common-duct exploration exist, is becoming increasingly evident. Welch,[35] in assessing this problem, pointed out that Allen[36] introduced the practice of thorough dilatation of tight sphincters of Oddi by Bakes dilators many years ago at the Massachusetts General Hospital. It was Allen's observation that when this practice was followed the number of patients with postcholecystectomy symptoms was greatly reduced. More recently Brush et al.[37] evaluated the results of dilatation of the sphincter of Oddi performed at the time of choledochostomy. They compared 198 patients who had dilatation of the sphincter at the time of choledochostomy with 230 controlled subjects who also had choledochostomy but no dilatation of the sphincter. They observed no case of re-formed or residual common-duct stones in the group in which dilatation of the sphincter was performed as compared with the finding of residual or re-formed stones in 10 of the 230 patients who had choledochostomy but no dilatation of the sphincter. They remarked that the hospital stay and the mortality were not increased by dilatation of the sphincter. Cole[38] described 3 patients with stenosis of the ampulla of Vater who were relieved of symptoms by transduodenal sphincterotomy. Doubilet and Mulholland[6] objected, on the other hand, to the use of such terms as "Odditis" and "fibrosis of the sphincter." In their opinion, "with rare exception, due to injury from passage of a stone or a large probe at previous operation it [the sphincter of Oddi] is not fibrosed or the seat of an inflammatory process." In this regard they were referring to patients with chronic pancreatitis. It is our belief that the occurrence of fibrosis of the sphincter of Oddi is not necessarily dependent upon either common-duct stones or previous operative manipulation of the distal end of the common bile duct. Walters[39] accepts the validity of stenosis of the sphincter of Oddi and advocates a transduodenal sphincterotomy for the relief of this condition. Cattell and Colcock[40] analyzed 49 cases of fibrosis of the ampulla of Vater and found that dilatation of the sphincter by Bakes dilators was employed in 35 cases and transduodenal sphincterotomy in 10. The long-limb T tube was employed in each procedure. Of 37 patients followed for six months or longer 28 had complete relief of symptoms, and 6 were improved; 1 patient received no benefit, and 1 subsequently died. Cattell, Colcock and Pollack[41] recently analyzed 100 cases of stenosis of the sphincter of Oddi observed at the Clinic, not including the initial 49 cases previously reported by Cattell and Colcock. The etiology is unknown, but, as these authors emphasized, in the long-standing cases the clinical impression is that of an inflammatory stricture and in 12 cases in which a biopsy was performed microscopical analysis showed chronic inflammation and fibrosis.

The clinical picture in these 100 cases was essentially that of recurrent attacks of pain in the right upper quadrant, with radiation to the middle or right subscapular area. In 84 per cent of this series pain was listed as severe. Forty-six of the 100 patients were jaundiced or gave a history of jaundice. It is interesting that this is about the same rate of jaundice as is observed in cases of proved common-duct stones. In addition, however, 13 patients had a questionable history of jaundice. Eighty-one of the patients had had a previous cholecystectomy without relief of the original symptoms. Forty of these 81 patients had had choledochostomy at the time of or after cholecystectomy. Twenty-one had had two, and 1 had had four previous operative procedures on the biliary tract. The serum bilirubin was elevated in half the patients. The alkaline phosphatase was elevated above 10 Bodansky units in a third and was slightly above normal in an additional third of the cases.

The preoperative detection of stenosis of the ampulla of Vater has been greatly facilitated by the

*From the Department of Surgery, Lahey Clinic.

†Director and surgeon-in-chief, Lahey Clinic; surgeon-in-chief, New England Baptist Hospital; surgeon, New England Deaconess Hospital.

‡Surgeon, Lahey Clinic; surgeon, New England Baptist and New England Deaconess hospitals.

advent of intravenous cholangiography. Wise and O'Brien[22] have pointed out the important intravenous cholangiographic features of stenosis of the ampulla, indicating that marked dilatation of the common duct (greater than 15 mm. in diameter) always meant common-duct obstruction and in the absence of demonstrable stones or stricture usually indicated the presence of fibrosis or stenosis of the sphincter of Oddi. They emphasize particularly, however, the fact that the time-density relations of the visualized ducts were equally significant and that in the presence of ducts less than 15 mm. in diameter the persistence of visualization without diminution in density at the end of a hundred and twenty minutes or more was indicative of obstruction. This time relation and density factor obtains only if the gall bladder has been removed or in the presence of cystic-duct obstruction with nonvisualization of the gall bladder. With the use of intravenous cholangiography the preoperative diagnosis is made not only with more assurance but also more frequently than before the discovery of this roentgenographic method.

Forty-seven patients in this group reported by Cattell, Colcock and Pollack had intravenous cholangiograms, and obstruction was noted in 33 of the 36 visualized ducts. In 11 cases nonvisualization was presumably caused by poor liver function. Jaundice was present in several of the nonvisualized cases.

The common bile duct was found to be dilated in 68 of 100 patients at the time of exploration. Calculi were found in 38 cases, and 30 of these 38 patients had, or gave a history of, jaundice.

The operative diagnosis of benign organic obstruction of the ampulla of Vater is made in this clinic if a 3-mm. Bakes dilator cannot be passed through the ampulla into the duodenum. If a dilator of small caliber does not pass readily into the duodenum, the duodenum and head of the pancreas are always mobilized to straighten out the distal end of the common bile duct and to facilitate the manipulation of the Bakes dilator within the terminal segment of the common duct.

Seventy-two of the 100 patients were treated by transduodenal sphincterotomy with implantation of a long-arm T tube. One patient had a transduodenal sphincterotomy with the implantation of a short-arm T tube. In 26 cases a choledochostomy with mechanical dilatation of the sphincter by graduated Bakes dilators was employed. We now consider this a less satisfactory method of treatment. A choledochojejunostomy followed by a choledochoduodenostomy was performed in 1 case. No significant postoperative complication attended 67 of the 73 operations in which transduodenal sphincterotomy was performed. Complications occurring in the 6 remaining patients included 2 cases of mild gastrointestinal bleeding, 1 of transient biliary fistula, which closed spontaneously, 1 of hepatitis and 2 of pancreatic necrosis developing postoperatively. One of the 2 patients with pancreatic necrosis died at home three and a half months later with a persistent pancreatic fistula. The other patient survived the pancreatic necrosis but now has evidence of chronic recurrent pancreatitis two and a half years after operation.

Two deaths occurred in the hospital, a mortality of 2 per cent. One was due to a cerebrovascular complication that followed operation. The other death resulted from far-advanced portal cirrhosis with hemorrhage from esophageal varices.

Eighty-one patients have had excellent results, 9 were improved by the operation, and 8 had poor results.

Preston[42] advocated transduodenal ampulloduodenostomy and retrograde exploration of the common bile duct in the management of obstruction of the choledochus by stones, stricture or stenosis of the distal end of the common bile duct. He reported retrograde exploration of the common bile duct in 38 cases. Transduodenal sphincterotomy was performed in 6, and an ampulloduodenostomy in 32 cases. The latter procedure apparently consists of passing a small malleable probe through the cystic-duct stump into the opened duodenum and then performing a sphincterotomy and subsequently suturing the edge of the duodenal mucosa to the epithelial lining of the common duct. The author noted stenosis of the distal end of the common duct sufficient to block the free passage of a 3-mm. probe in 30 of these cases.

It should be pointed out in this connection that stenosis is extremely frequent in this series in relation to the number of ducts explored. The practice of suturing the duodenal mucosa to the epithelial lining of the common duct in a circumferential manner after sphincterotomy entails some risk of injury or occlusion to the main pancreatic duct. Preston, however, observed no cases of jaundice, duodenal fistula or pancreatitis after this procedure. If the duodenal mucosa is to be sutured after sphincterotomy, the opening of the duct of Wirsung should be identified precisely, or the inferomedial aspect of the ampulla of Vater should be carefully avoided.

With the increasing interest in sphincterotomy it is important to point out that this operation should not be used indiscriminately and that when employed it should not be regarded lightly. Doubilet and Mulholland[1] reported 17 deaths in 319 cases of sphincterotomy, an operative mortality of 5.3 per cent. These operations, however, were performed for chronic relapsing pancreatitis rather than for stenosis of the sphincter of Oddi.

Choledochal Cysts

Shocket, Hallenbeck and Hayles[43] reported 6 cases of choledochal cysts observed at the Mayo Clinic. This report stresses the observation that the cysts are regarded as congenital in origin, that they are rarely

diagnosed preoperatively and that they may be easily misinterpreted at the time of abdominal exploration. The common clinical features of a mass in the right upper quadrant associated with abdominal pain followed by jaundice and frequently accompanied by chills and fever, particularly when they occur in a child, suggest the diagnosis of a choledochal cyst. The authors emphasized the fact that collected series of cases from 1900 to 1943 reveal a mortality of 87 per cent when the cyst was marsupialized or excised, and 30 per cent when the cyst was anastomosed to the duodenum. In the 6 cases observed at the Mayo Clinic there was 1 postoperative death in an eight-year-old patient in whom the cyst was excised and a choledochoduodenostomy was performed.

Gross[44] described 9 patients, 7 of whom survived an operation. One of the postoperative deaths accompanied an attempt at excision of the cyst. Of the 7 survivors in Gross's series, followed for three to nineteen years, only 1 was having difficulty. This was characterized by recurrent cholangitis and jaundice.

At the Lahey Clinic we have operated on 5 patients with choledochal cysts whose ages varied from three to thirty-two years. One of us (K. W. W.) recently operated on a three-year-old boy with an extremely large choledochal cyst that extended inferiorly beneath the head and neck and proximal body of the pancreas so that the most dependent portion was beneath the inferior aspect of the head of the pancreas. There was a small segment of relatively normal but dilated common hepatic duct. The cyst was anastomosed to a loop of jejunum with a diversionary enteroenterostomy. Postoperatively, the child ran a febrile course, which was relieved by external catheter drainage of a more dependent portion of the cyst. In this particular case it was not practicable to perform the anastomosis in the most dependent portion of the cyst, a principle that should be pursued whenever possible in the management of these uncommon and difficult problems.

Wounds of the Liver

Sparkman and Fogelman[45] reviewed 100 consecutive cases of liver injury admitted to a city-county general hospital.

Approximately half the patients in this series exhibited shock on admission. The liberal use of whole blood and intravenous infusion of saline solution was recommended as a preoperative measure. Early operation was advocated despite the fact that active bleeding had stopped spontaneously at the time of abdominal exploration in half the cases.

The highest mortality was observed in nonpenetrating crushing injuries or shotgun wounds. Hemorrhage represented the most common cause of death; the next most frequent causes were infection, necrosis and bile peritonitis.

The mortality in this series was 10 per cent and the morbidity 44 per cent. Careful débridement and adequate drainage are indicated in the presence of extensive fragmentation and destruction of liver tissue. Intensive, early antibiotic therapy is thought to improve the chances of survival and diminish the number of complications.

Operative Cholangiography

The controversy over the need for and the value of operative cholangiography continues. Hoerr[46] emphasized its value and advocated its use to demonstrate the presence or absence of common-duct stones, to determine the presence of obstruction or physiologic disturbance of the sphincter of Oddi, to identify or eliminate the presence of jaundice of hepatic origin and to delineate the location of benign strictures of the hepatic ducts. Gifford and Kahlstrom[47] reported an analysis of two separate series of 100 cases each of cholelithiasis treated surgically. In the first group of 100 cases, operative cholangiography was not employed, and the indications for opening the common duct were based entirely upon clinical and operative findings. The common duct was opened in 29 of the 100 patients. Stones were found and removed in 9, and no stones were found in the remaining cases, in which choledochostomy was performed. In the second group operative cholangiography was carried out in each case, and the common duct was explored in 27. In 23 of these 27 cases the indication for exploring the common duct was based upon cholangiographic evidence of stones, and stones were found in 21 of the 23 cases. In 2 cases air bubbles presumably accounted for the cholangiographic representation of stones. In the remaining 4 patients, in whom the cholangiogram showed no stones, the common duct was explored on clinical indications. Residual stones were proved in 6 patients and suspected in an additional 8 patients in the first group whereas, in the second, stones were proved to have been overlooked in only 3 patients. Baker[48] analyzed the problem of operative cholangiography and enumerated some of the considerations that must be taken into account when one is assessing this method of studying the common bile duct. He pointed out that special equipment is necessary and that the procedure requires some increase in operative personnel and demands upon the department of radiology. He emphasized, as all advocates of the procedure do, the fact that close co-operation between the radiologist and the surgical staff is necessary. The method is prone to greater technical error if it is used only occasionally. Baker agreed that operative cholangiography could demonstrate the patency between the biliary tract and duodenum and could determine the relative size of the extrahepatic and intrahepatic ducts and that it was quite valuable in study of the ductal system in infants operated upon for biliary obstruction. This procedure, according to Baker, is particularly useful during exploration for prolonged

jaundice thought to be due to hepatitis or intrahepatic obstruction from tumor.

Baker was less enthusiastic in relating this method of study to the detection of common-duct stones. In analyzing his material in this regard he pointed out that the common bile duct was explored in 40 per cent of patients operated upon for cholelithiasis and that stones were found in 20 per cent when the decision to open the common bile duct was made upon clinical and operative findings alone. He stressed the fact that the common bile duct was dilated to a diameter greater than 8 mm. in 72 of the 76 patients with common-duct stones, as well as in the 12 cases of fibrosis of the sphincter of Oddi, indicating that dilatation of the common bile duct was the most reliable operative finding demanding exploration. Baker suggested that operative cholangiography should be employed in patients with dilated common bile ducts in which the dilatation is thought to be compensatory, as in the presence of cystic-duct obstruction. He did not believe that fibrosis of the sphincter of Oddi could be reliably ruled out by cholangiography.

In view of the reported prevalence of retained common-duct stones, varying from 2 to 24 per cent in reported series, Baker advocated that when cholangiography was available it should be routine in all cases in which open choledochostomy has been done. This should be done to detect residual stones before the abdomen is closed.

Other favorable reports of operative cholangiography have been recorded by Swenson and Fisher,[49] by Hight and Lingley[50] and by Swedberg.[51]

Johnston, Waugh and Good[52] reported recurrent or persistent symptoms in 26 of 175 patients who had been operated upon for common-duct stones. Re-exploration was necessary in 15 of the 26 cases. Despite this rate of re-exploration these authors did not believe that operative cholangiography would have eliminated or materially reduced the number of retained stones.

Routine cholangiograms have not been employed in this clinic. This decision, as previously enunciated separately by Lahey[53] and Cattell,[54] has been based upon consistent adherence to certain practices and to the demonstrable results of this policy. In the first place the indications for common-duct exploration during operations for cholelithiasis have been sufficiently broad in concept and carefully adhered to in practice to reduce to a minimum the prospect that the common bile duct will not be opened when stones are likely to be present. The second is the practice of proving or affecting the adequate patency of the sphincter of Oddi each time the common bile duct is opened. The third factor is careful irrigation and exploration of the larger hepatic radicles as well as the distal portion of the common bile duct. Fourthly, adequate mobilization of the duodenum and head of the pancreas is resorted to in all cases of common-duct exploration in which any difficulty is encountered in dilating the sphincter of Oddi to a degree of patency that corresponds roughly to the diameter of the common bile duct itself. The fifth factor is the practice of transduodenal exploration of the papilla and distal end of the common bile duct in cases in which adequate dilatation of the sphincter cannot be accomplished through the choledochotomy. The sixth is the demonstration that the mortality and morbidity of exploration of the common bile duct is not materially greater than that for cholecystectomy alone. This opinion is borne out by the recent study of Colcock and McManus[30] indicating that, in an analysis of 1356 patients operated upon at the Lahey Clinic during a five-year period, the mortality of the entire group was 1.1 per cent. The mortality for cholecystectomy alone was 0.9 per cent, and that for cholecystectomy and choledochotomy was 1.1 per cent.

The importance of dilatation of the sphincter of Oddi was again emphasized recently by Brush and his associates,[37] by Walters[55] and by Welch.[56]

The editorial by Welch is an excellent appraisal of this problem, and places the responsibility for retained common-duct stones where it appears to us properly to rest — that is, upon the broad clinical indications for exploration of the common bile duct, a careful and precise technic for choledochotomy and an insistence upon the patency of the sphincter of Oddi every time the common bile duct is opened.

Strictures of the Common Bile Duct

Postoperative stricture of the common bile duct represents the most serious benign, acquired disease of the biliary tract. The large majority of postoperative strictures follow simple cholecystectomy. As more and more patients are subjected to cholecystectomy increasing numbers of patients with common-duct strictures are observed. Although it is impossible to say that the actual incidence of injuries to the common bile duct related to biliary-tract surgery has increased, it cannot be questioned that the number of common-duct injuries is much too great.

Donaldson, Allen and Bartlett[57] found, in analyzing 85 postoperative strictures, that the injury to the common bile duct followed cholecystectomy in 62 cases, cholecystectomy and choledochostomy in 19, gastrectomy in 3 and portacaval shunt in 1 case.

These authors related that in 80 per cent of these injuries to the bile ducts the gall bladders were removed in a retrograde fashion. In attempting to assess the factors that contributed to the injury of the ducts, they pointed out that of a total of 81 post-cholecystectomy strictures, only 30, or 37 per cent, were due to proved injury to the duct recognized at operation or discovered at laparotomy soon after the original procedure. In the remaining 63 per cent it appeared obvious to the authors that many of these ducts were partially occluded so that gross injury

probably accounted for many more of the strictures. They did believe, however, that the intensity of the original infection, the accumulation of blood or a collection of bile adjacent to the common duct probably accounted for some of these postoperative strictures. Cole and his associates[58] considered 66.3 per cent of 92 benign strictures in their series to have been caused by operative trauma; 22.5 per cent were thought to be secondary to inflammation. They, too, agreed that many of the strictures listed as secondary to inflammation were undoubtedly traumatic in origin.

Treatment

The real tragedy of strictures of the common bile duct does not rest entirely upon the extreme and protracted morbidity, the necessity for repeated operations in many cases, with attendant great economic loss, or upon the immediate and delayed postoperative mortality. The tragedy is that they are largely avoidable.

It is perhaps more important to emphasize methods of preventing common-duct strictures than it is to detail technical methods of reconstructing the bile duct. Although it may be true, as emphasized by Donaldson, Allen and Bartlett,[57] that these injuries are not always due to a hurried operation by an inexperienced surgeon working through an inadequate incision with poor anesthesia, it seems worth while to emphasize the fact that the seriousness of a common-duct stricture is so great that attention to these details should be stressed rather than minimized.

The controversy about whether the gall bladder can be more safely removed from the fundus downward or from the region of the junction of the cystic and common ducts toward the fundus will continue. It is more appropriate to point out that injury can occur to the common hepatic or common bile duct during either approach. One can be certain that the gall bladder can be safely removed only after one has demonstrated the cystic artery, the common hepatic duct, the junction of the cystic duct with the common bile duct and the common bile duct distal to the junction of the cystic and common bile ducts. Although it may be true, as contended by Glenn and Hays,[34] that it is safer to remove the gall bladder from the fundus toward the ampulla, the procedure is not sufficiently safe for the gall bladder to be removed in this fashion until all the structures enumerated above have been carefully delineated. It is possible in almost every case to demonstrate the distal part of the common bile duct in the supraduodenal region even in the presence of marked inflammatory reaction secondary to acute cholecystitis. If it then appears that dissection around the cystic artery, cystic duct and common hepatic duct will be unduly hazardous, the surgeon may elect to open the common duct where it has been exposed distally and insert a Bakes dilator proximally to delineate the common hepatic duct and particularly the right hepatic duct. With the Bakes sound within the lumen of the common hepatic duct it is often easy to proceed with the dissection about the cystic duct and cystic artery. If, however, with this dilator in place the common hepatic duct still cannot be delineated in the region between the cystic duct and cystic artery a cholecystostomy should be performed, subsidence of the inflammatory reaction being awaited before cholecystectomy as a staged procedure is done.

As pointed out by Lahey[59] it is pertinent in this respect to emphasize once more the anatomic fact that the cystic artery is shorter than the convoluted cystic duct and that undue tension on the ampulla of the gall bladder may cause a tear or avulsion of the cystic artery. The natural inclination is to grasp the bleeding area with a series of hemostats until the bleeding is controlled. It is far better under such circumstances to control the hemorrhage by compression of the hepatic artery as it runs near the free edge of the gastrohepatic omentum by inserting the index finger of the left hand into the foramen of Winslow and then compressing the hepatic artery between the index finger and the thumb of the left hand. By such compression, the accumulated blood may be aspirated from the field, and the point of injury or division of the artery identified and safely clamped. More occasionally venous bleeding in this area may lead to indiscriminate use of hemostats, with injury to the ductal system. It should be borne in mind that the venous pressure in the portal system under normal circumstances is extremely low and that although considerable blood may well up suddenly and obscure the entire field from such venous bleeding, this type of hemorrhage is easily controlled in most cases by simple pressure. The utilization of a small ribbon of Gelfoam, followed by pressure with a moist sponge, will almost invariably control this type of bleeding unless there is marked portal hypertension.

During any cholecystectomy an obvious or seeming anomaly of the biliary or arterial system around the gall bladder or bile ducts should not be considered lightly. When an anomaly is encountered, if its true nature is not easily and obviously delineated, it should be decided, before any vascular or ductal structure is clamped or divided, whether or not it is safe to proceed with the cholecystectomy. Frequently, it may be preferable to decide forthwith that cholecystectomy should not be pursued, particularly if the surgeon's experience in this field is limited. If after careful dissection the anomaly is not perfectly clear and compatible with safe cholecystectomy, choledochostomy should be performed, and if the anomaly cannot be explained by probing of the ducts, an operative cholangiogram should be obtained. If the interpretation of the cholangiogram is likewise confusing, the common bile duct should merely be drained, and a cholecystostomy performed and stones removed from the gall bladder. This will rarely be necessary.

Evaluation and Preparation for Surgery

The majority of patients with common-duct strictures experience marked weight loss and have moderate or severe jaundice. The importance of careful preoperative preparation in these patients may be decisive in determining the outcome after reconstructive surgery. Particular attention to this aspect of the problem has been recorded by Lahey,[59] Ravdin[60] and Cole.[61]

The marked weight loss reflects deficiencies in blood volume, serum proteins and total red-cell mass. The obstructive jaundice has usually been present sufficiently long to produce hepatocellular destruction, with resulting disturbance in prothrombin concentration and in protein synthesis. It is now known that these patients need a high-calorie intake with high-protein and high-carbohydrate fractions. They will tolerate moderate amounts of fat in the diet, and the inclusion of fats makes it easier to supply the adequate caloric intake orally in most cases. Supplemental intravenous infusion of glucose is used only in patients in whom adequate oral intake cannot be achieved. Efforts are directed toward restoring the blood volume to normal by multiple transfusions. These patients are given vitamin K intramuscularly to supplement the protein in the regular diet. Meritene feedings, 170 gm. between meals and at bedtime, are used routinely.

In evaluating these patients as operative risks and in determining the timing of their surgery one gives considerable attention to the presence of hepatocellular disease as reflected by the cephalin flocculation and thymol turbidity tests. A test that is found to be most helpful in determining response to treatment is the recovery of the prothrombin levels in patients in whom this factor has been significantly depressed initially. The persistence of a serum albumin below 3 gm. per 100 ml. is a particularly ominous sign. Cole, Ireneus and Reynolds[62] have emphasized the necessity of heeding evidence of marked deficiency of liver function in patients with common-duct stricture both in terms of adequate preparation and in the choice of a minimal procedure such as the establishment of an external biliary fistula instead of a definitive repair under these circumstances.

Another undesirable aspect of common-duct stricture and particularly of recurrent stricture is the ultimate development of portal hypertension. This complication not only invites massive hemorrhage from esophageal varices but also constitutes a real technical hazard both from increased blood loss and from interference with the anatomic visualization of the duct remnants. In several cases at the Lahey Clinic splenorenal shunts have been performed to obviate this difficulty. Some of these cases have been reported by Boyd.[63] Cole, Ireneus and Reynolds also emphasized the gravity of this complication, indicating that 29 of 122 cases gave evidence of portal hypertension and that 4 of these patients bled to death either from esophageal varices or from uncontrollable hemorrhage at the time of operation. These authors have also performed splenorenal decompression of the portal system both before and after common-duct repair.

Choice of Operation and Technical Considerations

Considerable controversy continues about the preferred method of repairing strictures of the common bile duct. Although most authors agree that theoretically, at least, it is preferable to achieve an end-to-end anastomosis of the damaged duct, with preservation of the sphincter of Oddi, all who have to deal with this problem in any numbers recognize that this goal cannot always be achieved. Lahey and Cattell have emphasized the fact that the percentage of patients in whom an end-to-end repair of the injured common bile duct can be achieved can be increased materially if the distal end of the common bile duct is secured by division of the head of the pancreas and utilization of the intrapancreatic portion of the distal duct for reconstructive purposes. When this duct can thus be secured and when it is not damaged by cholangitis, an end-to-end repair can usually be achieved despite a considerable defect in the duct itself since the head of the pancreas and duodenum can be widely mobilized to permit approximation of the divided segments of the duct.

Ravdin[60] agreed with this contention that it is worth while to preserve the sphincteric mechanism whenever possible. He cited the work of Fitts in determining the value of the sphincter in preventing ascending infection. In experiments on dogs Fitts and his associates[64] demonstrated that by exposing the bile ducts to virulent flora of the colon with and without an intact sphincter the results indicated protection from ascending infection when the sphincter mechanism was preserved.

Despite our conviction that whenever possible it is better to achieve an end-to-end anastomosis of the divided ends of the common bile duct, we agree with the contention that ascending cholangitis is a reflection more of obstruction than of reflux or regurgitation into the biliary system. Many surgeons prefer the Roux-Y hepaticojejunostomy when an end-to-end anastomosis cannot be performed, and among these are Cole and his associates[62] and Allen.[56] Cole pointed out in this respect that when the Roux-Y procedure is employed, the defunctionalized loop should be at least 36 cm. long. It is doubtful if a loop no longer than 36 cm. will prevent regurgitation into the biliary tree. On numerous occasions during barium studies after resection of the head of the pancreas in which an end-to-side gastrojejunostomy has been performed more than 36 cm. beyond the choledochojejunostomy, we have observed that barium not only refluxes into the liver but also fills the entire proximal loop of jejunum, which in some cases may be as long as 56 cm. If the same analogy is valid it should also be pointed out that in this large experience with re-

section of the head of the pancreas in which the biliary-intestinal anastomosis has invariably been done to a loop of the jejunum rather than by the Roux-Y method, we have observed no case of cholangitis except in the presence of stenosis of the biliary-intestinal anastomosis, which is an extremely rare occurrence in these cases.

Walters[65] usually employs a choledochoduodenostomy. In a report on surgery of the biliary system and pancreas for 1954 Hallenbeck et al.[66] indicated that 52 of 74 strictures were treated by anastomosis of the hepatic duct or common bile duct to the duodenum. Although the anastomosis was performed between the hepatic duct and jejunum in only 7 cases, end-to-end repair of the bile duct was done in 8 cases, an external biliary fistula was established in 6, and a plastic operation was done in 1.

Kirby and Fitts[67] reported on the experimental use of isolated sections of the jejunum employed to bridge the gap previously made by excision of a segment of the common bile duct in dogs. This method was appealing in that it provided tissue with an independent blood supply and a mucosal lining. They observed that stricture formation, biliary stasis and cholangiohepatitis did not occur in animals observed up to thirteen months after this type of repair.

Continuous efforts to find an appropriate method of bridging a gap in the common bile duct caused by traumatic injury will naturally be pursued in the light of frequent failure of current methods to achieve success. No one interested in this difficult problem would want to discourage such efforts, but it does seem, at present, that the crux of the matter is related more to the length and the character of the existing common hepatic duct than to the extent and condition of the distal end of the duct or the type of prosthesis or homologous replacement tissue to be employed. To state this in another way, a good result is likely if an adequate length of relatively normal common hepatic duct is available for anastomosis, regardless of whether the anastomosis is done to a relatively normal segment of distal duct to the duodenum or the jejunum by Roux-Y or loop hepaticojejunostomy. Frequently, however, the segment of common hepatic duct is so small (or, in some cases, nonexistent) that a favorable result cannot be anticipated even though the distal segment of the duct appears adequate for direct anastomosis. In our experience with this problem at the Lahey Clinic it is frequently necessary to divide the partition between the right and left hepatic ducts to achieve a sufficient length of common hepatic duct to permit anastomosis to the jejunum. In many cases either the injury to the duct has been above the bifurcation of the right and left hepatic ducts or, as a result of a process of natural attrition from repeated reconstructions, the remaining portion of the common hepatic duct has been completely fibrosed. It may be necessary either as a result of the height of injury or as a consequence of loss of common hepatic duct from repeated operative procedures to implant the right and left hepatic ducts individually. In rare cases a third duct, that draining the caudate lobe, may also have to be implanted independently.

Selection and Duration of Prosthesis

One of the continuing controversies over the technical aspects of common-duct repairs revolves about the choice of a prosthesis and the length of time it should be left in place. Historically, many substances have been utilized as an internal splint — namely, segments of rubber tubing, T tubes, rubber Y tubes, a variety of vitallium tubes and tubes made of silicon. All these prostheses have one common feature: if left in place sufficiently long they will all in turn become encrusted with cholesterin and bile pigment crystals and become occluded. We have had an opportunity at the Clinic to utilize all these prostheses, and currently one of a variety of rubber stents is employed in the reconstruction of the common bile duct. When an end-to-end choledochocholedochostomy is utilized in the reconstruction of the common duct it is customary to employ the long-limb T tube[68] with the long distal limb traversing the sphincter of Oddi and lying in the duodenal lumen. The conventional short-limb T tube may be employed if the stricture is of minor degree. Although one may be loath to employ an indwelling Y tube, knowing that in time it will become occluded, this choice may still be the preferred one in recurrent common-duct stricture if the segment of common hepatic duct is extremely short and it has been necessary to divide the septum between the right and left hepatic ducts to obtain a longer segment of common hepatic duct.

Some interest has been manifest in attempts to evaluate the effects of leaving a prosthesis in the common duct in terms of encouraging fibrosis and recurrent stricture. In an experimental study by Madden and McCann[69] the results indicated that the longer the prosthesis was left in place, the more likely was the associated fibrosis, cholangitis and recurrent stricture. Our experience on a clinical basis does not bear out this experimental observation, and it has been our practice based upon this clinical evaluation to leave these stents in place when they are amenable to external control for a period of six to twelve months. In general, it has appeared that the larger the caliber of the prosthesis employed, the better the result. We have observed, of course, evidence of obstruction of these prostheses, but usually signs of obstruction in this regard have also indicated the presence of recurrent stricture.

Lary and Scheibe[70] have reported an experiment showing that less fibrosis and less stricture develop in laboratory animals in which an end-to-end anastomosis of the common duct has been done if no prosthesis is utilized. Cole[61] believed that in the absence of significant inflammatory changes in human strictures of the common duct, no prosthesis should be

used. He does think, however, that in the presence of a thickened and inflamed duct wall a prosthesis should be employed for eight to ten months. In our experience most of these ducts are thickened, edematous and inflamed.

Results of Surgical Treatment of Common-Duct Strictures

The ultimate result of the surgical repair of strictures of the common duct is difficult to assess, for there is available no group of patients with traumatic injury to the common duct who have been followed through the life history of the injury. Although interim analyses of large series appear in the literature indicating good results in a variety of surgical repairs of common-duct strictures in 60 to 75 per cent of cases, it should be borne in mind that if these patients are followed through an entire generation, an unpredictable number of recurrences will appear in the group who, at the time of interim survey, had been placed in the favorable results.

What is known is that the consequence of an injury to the bile duct is grave; that the repair of these injuries requires considerable technical skill and a wide experience in biliary-tract surgery to offer the patient a reasonable prospect of cure; that each successive operation involves an unavoidable attrition in terms of loss of remaining common-hepatic-duct substance; that some of these patients are poor candidates for definitive surgery and are best treated by the establishment of an external biliary fistula as an initial procedure to be followed at an appropriate interval by an attempt at reconstructive repair. The composite picture of common-duct stricture is one of such sad proportion as to demand increasing emphasis upon its prevention and continued efforts to improve the results of surgical repair of these injuries. The room for progress in the area of prevention is much greater than the prospect of increasing the technical methods of repair or of finding the ideal prosthesis or an adequate heterogenous or homologous substitution for the injured common bile duct.

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MEDICAL INTELLIGENCE

ALOPECIA TOTALIS AFTER DESACETYLMETHYLCOLCHICINE THERAPY OF ACUTE GOUT*

Report of a Case

WILLIAM M. MIKKELSEN, M.D.,†
ROLFE W. SALIN, M.D.,‡ AND
IVAN F. DUFF, M.D.§

ANN ARBOR, MICHIGAN

DESACETYLMETHYLCOLCHICINE, a crystalline alkaloid prepared from the bulbs of *Colchicum autumnale* and closely related structurally to colchicine, has recently been introduced for clinical trial in certain hematologic disorders and in acute gout. Several preliminary reports[1,2] have indicated that this agent is effective in the management of acute gout and that gastrointestinal side effects may be less marked than with colchicine. We wish to report a patient with gout treated with this preparation during an acute attack in whom alopecia appeared as a complication.

CASE REPORT

A 51-year-old man had a history of recurrent acute episodes of arthritis since the age of 39. Because of increasing frequency and severity of attacks he was referred to the University of Michigan Hospital in May, 1950. The diagnosis of nontophaceous gout was established on the basis of the typical history, a prompt clinical response to colchicine and a serum urate level of 7.5 mg. per 100 ml. (method of Block and Geib[3]). On 0.5 mg. of colchicine twice daily the patient did reasonably well, averaging 2 or 3 acute attacks each year. In February, 1954, multiple tophi were observed over the fingers and in the olecranon bursae. Probenecid (Benemid), 0.5 gm. twice daily, was added. For financial reasons the patient was irregular in his program of medication and in his attendance in the Arthritis Clinic. His tophi were observed to increase in size and number, and the acute attacks continued at a rate of 2 to 4 per year.

He was seen on November 15, 1955, because of an acute attack of 6 days' duration involving the left hand and wrist. This had not been relieved by oral administration of colchicine, 0.65 mg. every hour for 12 doses, although this therapy had produced severe abdominal cramping and nausea. Examination revealed marked swelling of the 1st, 2d and 3d metacarpophalangeal joints of the left hand, with increased heat and a dusky, erythematous discoloration of the overlying skin. Motion of the left wrist or fingers was impossible because of pain. Starting at 3 o'clock on the afternoon of admission 1 mg. of desacetylmethylcolchicine (Colcemide) was given orally every hour for 12 doses. On the following morning the patient experienced mild nausea, but no other gastrointestinal symptoms. The swelling and tenderness had decreased moderately, and he was able to move the left hand slightly. Desacetylmethylcolchicine was continued in a dosage of 1 mg. every 2 hours, but had to be stopped after 2 doses because of nausea, vomiting and profuse watery diarrhea. By the morning of November 17 these symptoms had been controlled with paregoric, and the left hand appeared unchanged. Colchicine, 0.65 mg. orally every 4 hours, was started. This was well tolerated, but during the night pain and inflammation in the left hand increased markedly. On the next morning prednisone, 60 mg. daily, was added. There was a prompt clinical response, and the prednisone was gradually reduced. The patient was discharged after 13 days, still on low doses of the steroid as well as maintenance colchicine and probenecid therapy. No change in blood values had been observed.

At the time prednisone was discontinued and approximately 2 weeks after the last administration of desacetylmethylcolchicine, he became aware of excessive amounts of hair in his comb. When seen 4 days later he estimated that 90 per cent of his scalp hair had been lost. The few remaining strands could be easily extracted manually. Hair in the other body areas, including the eyebrows, was not affected, and there was no skin rash. Colchicine and probenecid were continued, and no therapy was advised for the alopecia. By December 23 the hair had stopped shedding, although no regrowth was apparent until about January 1, 1956. By March 6 approximately 35 per cent of the scalp hair had regrown.

DISCUSSION

The occurrence of alopecia in association with desacetylmethylcolchicine therapy has been observed by others.[4-9] Leonard and Wilkinson[7] noted "some loss of scalp hair" in 1 of 8 patients with chronic myeloid leukemia receiving 3 to 10 mg. daily. Bock and Gross[8] described transient hair loss in 4 of 20 patients with leukemia receiving up to 20 mg. orally or 16 mg. intravenously a day. Piney,[9] in a report of a patient with chronic myeloid leukemia treated with a maximum of 15 mg. daily, stated that after approximately four months of therapy "there was a remarkable loss of hair, but, in spite of continued big doses this ceased . . . and the hair has regrown again."

Kuzell, Schaffarzick and Naugler[1] described 20 patients with acute gout treated with 1 to 4 mg. of desacetylmethylcolchicine intravenously a day, for one or two days in most cases. They observed a "good" response in 15 patients and diarrhea in only 2. Colsky, Wallace and Banowitch[2] discussed 10 patients with acute gout given a total of 5 to 8 mg. of desacetylmethylcolchicine orally. A satisfactory clinical response was obtained in 9 of the 10 cases. The only side effects were a maculopapular eruption in 1 and anorexia in 1. In neither of these groups did alopecia occur.

SUMMARY AND CONCLUSIONS

A case is reported in which 14 mg. of desacetylmethylcolchicine (Colcemide) was administered orally within a twenty-four-hour period for treatment of

*From the Rackham Arthritis Research Unit and the Department of Internal Medicine, University Hospital, and the Department of Dermatology and Syphilology, University of Michigan Medical School.

†Instructor in internal medicine, University of Michigan Medical School; associate physician, Rackham Arthritis Research Unit, University Hospital.

‡Instructor, Department of Dermatology and Syphilology, University of Michigan Medical School.

§Associate professor of internal medicine, University of Michigan Medical School; physician-in-charge, Rackham Arthritis Research Unit, University Hospital.

acute gout with the subsequent loss of all scalp hair. Previous cases of alopecia associated with desacetylmethylcolchicine therapy have been reported in patients with leukemic disorders, most of whom received larger total doses over longer periods. Further experience must be obtained with this drug before it can be considered a satisfactory substitute for colchicine.

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NONTHROMBOCYTOPENIC PURPURA DUE TO MILTOWN (2-METHYL-2-N-PROPYL-1,3 PROPANEDIOL DICARBAMATE)*

W. J. Carmel, Jr., M.D.,† and T. Dannenberg, M.D.†

Walnut Creek, California

Recently several new drugs have come into widespread use for their sedative or tranquilizing effects. The most widely publicized of these drugs is marketed under the trade names of Miltown and Equanil (2-methyl-2-n-propyl-1,3 propanediol dicarbamate).

The pharmacology of this compound, which is related to mephenesin, has been studied by Berger[1] and Hendley, Lynes and Berger.[2] Its clinical use was reviewed by Selling[3] and Borrus.[4] The former reported 3 allergic reactions involving fever, urticaria and angioneurotic edema, among 187 patients; the latter observed no hematologic changes in 104 patients and did not mention allergic reactions.

The object of this paper is to report a more serious type of reaction to Miltown manifested by purpura, edema and erythema. Within the past three months we have seen 3 remarkably similar cases of drug sensitivity to small amounts of this compound.

Case Reports

Case 1. H.E.R., a 37-year-old woman, was under observation for an unexplained anemia, which later was thought to be due to exposure to various benzene derivatives. All medication was discontinued on December 6, 1955, in an effort to make a definite diagnosis. On December 19 she was seen for symptoms of an acute anxiety reaction and was given Miltown, 400 mg. 3 times daily. After taking 2 tablets she immediately noted generalized pruritus with petechial dermatitis, first over the thighs and inguinal region and later involving the arms, hands and feet. The thighs and buttocks were diffusely swollen and erythematous, and the arms, shoulders and legs were covered with small petechiae and purpuric areas, chiefly in dependent portions. The liver and spleen were not palpable, and the remainder of the physical examination was not remarkable.

A capillary-fragility test was markedly positive. The hemoglobin was 12.1 gm. per 100 ml., the white-cell count 8300, and the platelets 260,000. The bleeding time was 4½ minutes, Lee–White coagulation time 11 minutes, and clot retraction complete in 2½ hours.

The dermatitis subsided without specific therapy within 3 days, when capillary fragility was within normal limits. Medication before December 6 included vitamin B_{12}, Folbesyn, Theragran, Nembutal, Sur-Bex and aspirin at various times, without untoward reactions.

Case 2. A.E.B., a 42-year-old woman, had excision of a chalazion on February 16, 1956, under local anesthesia. At a follow-up visit on March 15 she was given Miltown, 400 gm. 4 times a day, for insomnia and tension. After taking 3 tablets she noted a feeling of warmth of the inner thighs and axilla. On the next morning she discovered a widespread purpuric dermatitis of the thighs, trunk, abdomen and arms, together with anorexia, chills and fever. There was edema and generalized erythema of both thighs. The largest purpuric areas were in the dependent areas of the legs, but petechiae were present over most of the body. The platelet count was 470,000, and the white-cell count 14,800, with a normal differential. The bleeding time was 2 minutes, Lee–White coagulation time 14 minutes, and clot retraction complete in 2 hours. Capillary fragility was moderately increased.

She denied taking medication of any type for the preceding six months. Because of the severity of the reaction prednisone, 10 mg. 3 times a day, was prescribed. The purpura, edema and erythema cleared gradually in 1 week without further incident.

Case 3. W.V.R., a 50-year-old man, had been well except for a past history of duodenal ulcer. Because of a recent feeling of tension he took 1 tablet of Miltown, 400 mg., on February 27, 1956. This was given by his wife, a nurse. He noted the onset of a chilling sensation within 2 hours and stated that he also "felt feverish." On the next morning he noted a rash involving the lower legs. The rash became progressively worse, and he was seen approximately 20 hours after ingestion of the drug. He had not taken any other medications.

Physical examination showed an erythematous, purpuric rash extending from the ankles to the waist area. There was mild pitting edema, and the skin was warmer than the noninvolved areas, but there was no fever. He had a markedly positive capillary-fragility test. The hemoglobin was 15.9 gm. per 100 ml., and the white-cell count 7400, with 65 per cent neutrophils, 19 per cent lymphocytes, 10 per cent monocytes and 6 per cent eosinophils. The sedimentation rate was 17 mm. per hour, the bleeding time 1½ minutes, and the capillary tube-coagulation time 2 minutes; clot retraction was complete within 3 hours. The prothrombin time was 14 seconds for both patient and control. The platelets appeared within normal limits on blood smear.

The patient was given Benadryl, and the rash was completely gone within 3 days. Capillary fragility returned to normal on the following day.

Discussion

The acute onset of purpura and other evidence of increased vascular permeability in these cases was typical of an allergic shock organ response.

*From the departments of Medicine and Allergy, Kaiser Foundation Hospital.

†Staff member, Kaiser Foundation Hospital.

The normal platelet counts distinguish these cases from drug-induced thrombocytopenic purpura, notably to sedormid, organic arsenicals and quinidine, which may also occur and with similar rapidity.

In all 3 patients the dramatic onset of symptoms caused them to discontinue the drug immediately and to seek medical aid. Whether or not more serious complications would have ensued if the medication had been continued is unknown.

Summary and Conclusions

Three cases of acute nonthrombocytopenic purpura secondary to Miltown are presented. None of these patients had a past history of purpura, allergy or drug sensitivity. All the reactions occurred after 1 to 3 tablets were administered for the first time.

All patients given this drug should be forewarned of the possibility of untoward reactions.

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BRIEF RECORDING

Observations on Urticaria in Childhood

Isaac Hillson Schwartz, M.D.*

New Bedford, Massachusetts

IT is not uncommon for physicians treating children to be confronted with an eruption consisting of large, red macules with central whealing or swelling of sections of the body, or both. The former corresponds to the usual description of urticaria, and the latter to that of angioneurotic edema. Characteristic is also the shifting, fleeting nature of the individual lesions. It is customary to attribute these manifestations to sensitivity, usually to a hypothetical allergenic food.

In reflecting on this phenomenon, I remembered that almost all the cases met with in the course of a general pediatric practice cleared in about three days. As time went on, it also became apparent that recurrences were extremely rare. It was further noted that the response to antihistaminics was seldom convincing, although subcutaneous injection of epinephrine was frequently of transitory benefit. These characteristics hardly seemed consistent with the theory that such "hives" are of allergic origin. A review of the *Quarterly Cumulative Index Medicus* and of the *Armed Forces Current List* failed to reveal any pertinent writings, so that records were kept of all cases for which I was consulted from October, 1954, to March, 1956. This comprised a total of 27 cases.

*Medical officer, New Bedford Board of Health; junior pediatrician, St. Luke's Hospital; pediatrician, Sol-e-Mar Hospital (South Dartmouth).

Frequency of Recurrence

Of the 27 patients studied, only 5 had recurrences; 3 of these had more than one. These data were authenticated shortly before this article was submitted for publication.

Seasonal Incidence

During the eighteen-month study period, no more than 3 cases occurred during any single month, so that the seasonal distribution was a fairly random one.

Laboratory Findings

Initially, whenever possible, blood counts were carried out, but since none of these studies (a total of 13) revealed either leukocytosis or eosinophilia, it was decided to abandon this added burden to the patient.

Duration

Three cases lasted for one, 8 cases for two, 5 cases for three, and 2 cases for four days, and 8 cases for a week or more.

It will be noted that, on the basis of duration, the cases are divided into two broad groups: those with a median duration of two or three days and those with a duration of a week or more. The thought arises that the etiology of the former may be different from that of the latter.

Discussion

The rarity of recurrence and the lack of eosinophilia (as well as the failure to respond to antihistaminics) make it appear unlikely that most childhood urticaria is due to an allergic response.

In its epidemiology, which is characterized by spotty distribution, a course of approximately three days, occasionally associated fever or mild respiratory symptoms, and the rarity with which other members of the family are affected, it corresponds most closely to a viral disease of the type of roseola. In other words, it is quite possible that a previously unrecognized specific exanthem is involved.

Conclusions

Urticaria in childhood usually does not seem to be of allergic origin.

It is possible that in most cases it is a manifestation of a specific exanthem of unknown but infectious etiology.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42421

PRESENTATION OF CASE

A fifty-one-year-old toothpick manufacturer entered the hospital because of epigastric pain.

FIGURE 1. *Right Anterior Oblique View, Showing Thickened Folds in the Stomach and Duodenum, with a Question of Both Gastric and Duodenal Ulcers.*

One month previously he noted a persistent, nonradiating, dull epigastric "ache" that first appeared when he changed position and was unrelated to meals. Subsequently, the "ache" became almost constant. It was aggravated by a shift in position and accompanied by tenderness in the epigastrium. There were no other gastrointestinal symptoms. During the two months before admission he had lost 15 pounds in weight.

Physical examination showed a well nourished man in no distress. The chest was normal. Examination of the abdomen revealed an irregular, tender epigastric mass, 3 by 2 cm., that was fixed to the anterior abdominal wall just to the left of the mid-line. Peristalsis was normal.

The temperature was 98.2°F., the pulse 84, and the respirations 16. The blood pressure was 100 systolic, 60 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 13 gm. per 100 ml. and a white-cell count of 7400. The total protein, albumin, globulin and alkaline phosphatase were normal. The prothrombin content was 55 per cent. Three stool specimens were light brown and gave negative guaiac tests. X-ray films of the chest were normal. An upper gastrointestinal series demonstrated a small hiatus hernia of the sliding type that emptied well; the gastric folds were slightly increased in prominence; the folds in the duodenal cap and loop and in several loops of proximal jejunum were quite prominent; the duodenal cap appeared deformed in its middle portion (Fig. 1).

An operation was performed on the third hospital day.

DIFFERENTIAL DIAGNOSIS

DR. FRANK C. WHEELOCK, JR.,*: The protocol says the patient was "a toothpick manufacturer," which is an interesting bit of information. I do not believe it has any relation to the illness.

I should like to ask someone who might have known this patient what the character of the pain was.

DR. CLAUDE E. WELCH: It was an indefinite pain. It was never severe, nor did it have any special characteristic. The patient could not tell at what time of day it would occur. Pressure on that particular area, however, was slightly painful.

DR. WHEELOCK: How large was the man?

DR. WELCH: He weighed about 115 pounds.

DR. WHEELOCK: The mass was intraperitoneal, or at least below the surface of the abdominal wall.

DR. WELCH: Yes.

DR. WHEELOCK: May I see the x-ray films?

DR. JOSEPH HANELIN: The chest was normal, as the protocol states. In the gastrointestinal films (Fig. 1) — and this is another situation in which the radiologist would like to have done the fluoroscopy himself, to appreciate more fully what is shown on the films — I am impressed by the distinct increased prominence of the folds in the stomach. Gastric emptying was obviously quite rapid. I also wonder whether there may not have been an ulcer or ulcers of the stomach that were not easily demonstrated. On

*Assistant surgeon, Massachusetts General Hospital.

the film taken with the patient in the oblique position there are several pools of barium, which, if they do not represent superimposed loops of small bowel, may represent ulcers. There is enough irregularity of the posterior wall of the stomach and adjoining lesser curvature along the body to make me wonder if this is a malignant change; again, that is something that one can determine better at fluoroscopy. The folds in the duodenum are distinctly thickened; there may even be a small duodenal ulcer. In general, the picture is that of a gastroduodenitis with a possible duodenal ulcer, although the appearance of the stomach raises the possibility of a malignant process of some sort.

DR. WHEELOCK: The protocol mentions thick folds of the upper jejunum. Where are they, and what do they mean?

DR. HANELIN: I am not certain of any change in the mucosa of the small bowel. This appearance may be caused, among other things, by flooding of the small bowel by the rapid emptying of the stomach. Certainly, in portions where there is less barium in the jejunum the mucosal pattern is not abnormal. There seems to be thickening of folds throughout the major portion of the duodenum.

DR. WHEELOCK: There is no displacement of the stomach in any direction by any mass in front or behind it?

DR. HANELIN: No.

DR. WHEELOCK: Are these thickened folds the type seen with lymphoma of the stomach or duodenum?

DR. HANELIN: That is a distinct consideration, particularly since with lymphoma there may be preservation of pliability and the mass may present as thickened folds.

DR. WHEELOCK: You would say the x-ray findings are consistent but not diagnostic of lymphoma?

DR. HANELIN: I think that is true.

DR. WHEELOCK: Where are these folds located?

DR. HANELIN: There are several areas: one in the lower portion of the fundus and several along the body, which could be due to ulceration.

DR. WHEELOCK: The protocol mentioned a hiatus hernia.

DR. HANELIN: There is a hiatus hernia, which is fairly small.

DR. WHEELOCK: What percentage of the population have a hiatus hernia like this, symptomatic or asymptomatic?

DR. HANELIN: It depends on the age of the patient. In middle and old age perhaps 30 per cent of the patients have a hernia of this size; smaller hernias may be present in a greater percentage.

DR. WHEELOCK: Like diverticulosis of the colon, in this age group it is a very common finding and usually not clinically significant.

DR. HANELIN: That is true; it is a liability of age.

DR. WHEELOCK: To review the laboratory work first, the hematologic findings, being normal, are no help to me. The liver-function tests — the total protein, albumin-globulin ratio and the alkaline phosphatase — were normal, which certainly precludes obstruction of the common duct and, since there was no jaundice, also rules out primary liver disease. A prothrombin time of 55 per cent actually means that the intervals between the clotting of the patient's blood and of the blood used for control were perhaps only 2 or 3 seconds apart; I do not believe that that interval is of significance. The negative stool guaiac tests on several occasions make it unlikely that the patient had a carcinoma of the stomach or intestines, but certainly do not rule it out. We have all seen carcinomas in these areas when guaiac tests on the stools were negative.

The differential diagnosis will have to depend primarily on the history and physical examination. This man, even if he had no mass, certainly had some condition that I am sure should have been investigated by operation. Even if no disease were found at operation, I do not think that one should regret recommending, to a patient who has lost weight and has had epigastric distress of this kind for several months, an exploratory laparotomy when all the x-ray and chemical studies and even the physical examination are negative.

What are the possibilities that are presented by the history alone? First, because the epigastric distress persisted, was aggravated in a vague way by motion and was not related to what he did or what he ate, one thinks of disease of the pancreas. This could have been a chronic, localized pancreatitis. It would be unusual for this to occur without an initial acute attack of pain and symptoms of acute pancreatitis, followed by epigastric distress. With pancreatitis one would expect more pain across the abdomen and to the back than the patient had, but this would not be necessary. He could have had some peculiar abscess in the lesser omental cavity or somewhere in that vicinity, perhaps from a localized perforation of an ulcer or some inflammatory process in the pancreas or other nearby organs.

To blame the gall bladder for this is going far afield, but it might serve to point out that the symptoms one might expect from lesions of the gall bladder are not of this type. I am impressed by medical students' lack of knowledge of the type of pain that accompanies disease of the gall bladder. They always say that the pain is colicky. If one asks, "What is colicky?" they reply, "Colicky is crampy." A cramp is a pain that grabs the patient and then goes away repeatedly. That is certainly not the type of pain produced by disease of the gall bladder. Biliary-tract pain persists and worsens steadily until the stone slides out of the site that it is blocking or until the physician gives morphine. Pain from disease of the gall bladder

could hardly persist for a month without growing better or worse as the pain did in the case under discussion.

An abscess or cyst of the liver that produced this type of discomfort in the epigastrium is a remote possibility.

On the basis of the history, alone, what type of tumors could cause this kind of trouble? The patient was tender in the epigastrium; he apparently discovered, himself, that it hurt to move. One might think that a tumor should not cause these symptoms, but tumors can be extremely tender. Recently, I saw a carcinoma of the pancreas that had produced an exquisitely tender mass in the epigastrium. Carcinoma of the pancreas, of the stomach or of other organs in this area, particularly if they are rapidly growing, can become quite tender and uncomfortable. Carcinoma of the pancreas would account readily for the weight loss; most patients with carcinoma of the pancreas are admitted to the hospital with a history of weight loss; very few have a significant anemia. A carcinomatous metastasis to the liver can cause discomfort and pain with motion if it is resting against the peritoneal surface. The origin of the tumor may be in the stomach, the pancreas, gall bladder, colon and so forth.

When I first read the protocol, carcinoma of the stomach seemed unlikely, but since Dr. Hanelin indicated that there may be some changes in the stomach noted in the x-ray examination, it seems more likely. Certainly, the x-ray films are not infallible in the diagnosis of a carcinoma or tumors of various kinds in the stomach, for they may not show the mass in the proper profile for an accurate diagnosis.

Metastatic disease of the round ligament or the peritoneum in this area of the upper abdomen can be quite uncomfortable and can produce the symptoms that the patient had. Enlarged retroperitoneal lymph nodes, particularly those involved by lymphoma, can cause epigastric discomfort and weight loss. Cysts of the pancreas, the round ligament or other nearby structures can cause discomfort and this clinical picture. Cysts of the pancreas in more than half the cases are accompanied by weight loss.

When I first read the protocol I thought of a mass involving the abdominal wall, itself, such as an epigastric hernia or a tumor in the abdominal wall, but Dr. Welch has told me that this mass was beneath the abdominal wall.

The second approach to the problem is to consider how the mass itself felt and to disregard the history. What structure inside this area of the abdomen could feel this way? Did the mass move with respirations?

DR. WELCH: Very slightly.

DR. WHEELOCK: We have already pointed out that it did not protrude above the surface of the fascia. Was it very tender or slightly tender?

DR. WELCH: Slightly tender.

DR. WHEELOCK: Masses of the pancreas and even retroperitoneal lymph nodes, if they are enlarged enough and placed far enough anteriorly, can move with respiration. The fact that the mass moved with respiration, therefore, does not exclude the two possibilities that I have previously mentioned. Since almost any kind of tumor, if rapidly growing, can be tender, the various cancers suggested by the history are not excluded by the tenderness. The various inflammatory processes, however, are also perfectly consistent with the type of mass that was felt. Among those are pancreatitis of a smoldering nature and smoldering abscess of the lesser omental bursa. The fact that the mass was irregular makes abscess less likely than tumor because an abscess usually has a smooth contour.

It would be difficult to make the correct diagnosis even if I could feel the mass myself. I think the most likely diagnosis is carcinoma of the pancreas. In addition, the patient had a diaphragmatic hernia and probably had an old duodenal ulcer. My second choice is carcinoma of the stomach, with or without local metastases.

DR. RICHARD B. COHEN: Dr. Quinby, do you have any comment?

DR. JOHN T. QUINBY: I wondered how seriously to take the statement that the mass was fixed to the anterior abdominal wall; is that consistent with carcinoma of the pancreas or stomach?

DR. WHEELOCK: I do not think it is, but I do not know how one can be sure that it really was anatomically fixed. A mass in the pancreas that was adjacent to the anterior abdominal wall might invade it.

DR. EARLE M. CHAPMAN: I am intrigued by the first line of the history, which states that the patient was a fifty-one-year-old toothpick manufacturer; I cannot imagine a man who made toothpicks without sampling them. He may have swallowed a toothpick that produced a foreign-body reaction. Certainly, a toothpick would not show in the x-ray films.

DR. HANELIN: No; it would not.

DR. CHAPMAN: This patient reminds me of a man who recently came to me because of angina. He had been on the golf course and suddenly had substernal pain that was worse on exertion and when he swung his arms playing golf. He was sixty-four and had retired. All his friends were dying with occlusion of the coronary arteries so he was convinced that he had it. I could not make the diagnosis and arranged for him to see Dr. Paul D. White. Between the time that I saw him and his appointment with Dr. White x-ray films were taken. Exactly under the area of the pain was a pin. When I reviewed the history with him he recalled that he had swallowed the pin at a birthday party.

DR. WELCH: This man, although he was called

a toothpick manufacturer, actually was a politician and was in the midst of a campaign. He had many additional positions, including the presidency of a toothpick company.

DR. CHAPMAN: He probably was a nervous man who chewed toothpicks.

CLINICAL DIAGNOSIS

Carcinoma of stomach.

DR. FRANK C. WHEELOCK, JR.'S, DIAGNOSES

Carcinoma of pancreas.
Diaphragmatic hernia.
Duodenal ulcer, old.

ANATOMICAL DIAGNOSIS

Chronic pericolic abscess containing toothpick.

PATHOLOGICAL DISCUSSION

DR. COHEN: Dr. Welch, will you tell us the preoperative opinion and the findings at operation?

DR. WELCH: This man was a very plain-spoken fellow. We talked about diagnoses. I recalled a case somewhat like this that Dr. Joe V. Meigs had seen many years ago. That man had had a perforation of the bowel from a porcupine quill. I asked this patient whether he had been around any porcupines, but he had not. He wanted to know what I thought the diagnosis was, so I told him that he probably had carcinoma of the stomach; his physician, a close friend of the family, had already told him the same thing. After relatively few studies to exclude the unusual causes of loss of weight, I explored him. It was a relief to find that I was wrong. There was an inflammatory mass located close to the greater curvature of the stomach that was adherent to the anterior abdominal wall. On dissection of the mass we found that it ran down and was closely adherent to the colon. No diverticula could be uncovered in the colon, so we began to suspect the correct diagnosis. We finally excised the whole area, including a small segment of colon.

FIGURE 2

DR. COHEN: The specimen consisted of a mass of inflammatory tissue, 7 cm. in diameter (Fig. 2). Some of the tissue was firm and fibrous, suggesting that it had been present for some time. In the center of the mass were two pieces of toothpick, surrounded by yellow, necrotic débris. The mass was densely adherent to the transverse colon, and a fistulous tract leading from the colon was the point of egress of the toothpick into the peritoneal cavity.

The microscopical slides revealed dense, fibrous tissue and areas of neutrophilic infiltration with abscess formation.

CASE 42422

PRESENTATION OF CASE

First admission. A forty-four-year-old former laundry worker was admitted to the hospital because of a cough.

Three months previously he noted that his usual mild, intermittent cough became severe, continuous and productive of about a cupful of clear, watery, nonfoul-smelling sputum daily. Two months before entry he noted a mild, dull, nonradiating pain in the right side of the chest anteriorly that was associated with coughing. There were several episodes of hoarseness. There were no chills, fever, night sweats, hemoptysis or loss in weight.

He smoked 3 packages of cigarettes daily until two years before admission, when he stopped smoking because of irritation of the throat.

Physical examination revealed a well nourished man who coughed continually. Diffuse, moist, sticky rales that did not clear after coughing were audible over both lung bases.

The temperature was 98.6°F., the pulse 82, and the respirations 18. The blood pressure was 120 systolic, 80 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 16.2 gm. per 100 ml. and a white-cell count of 7600. The nonprotein nitrogen was 19 mg., the total protein 6.7 gm., the albumin 4.4 gm., and the globulin 2.3 gm. per 100 ml. The carbon dioxide was 28 milliequiv. per liter. The vital capacity was 3.1 liters. A smear of the sputum was negative for acid-fast bacilli. The tuberculin test (second-strength PPD) and the blastomycin, coccidioidin and histoplasmin skin tests were negative.

Cytologic examinations of the sputum were positive for malignant cells that were consistent with adenocarcinoma. X-ray films of the chest (Fig. 1) demonstrated discrete rounded densities measuring from several millimeters to 1 cm. in diameter that filled the lower and middle fields of both lungs; the medial portion of the right leaf of the diaphragm and the lower border of the heart were obscured by a density that filled the cardiophrenic angle; aerated bronchi

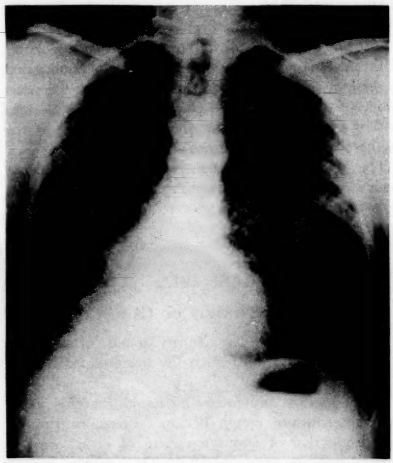

FIGURE 1. *Roentgenogram of the Chest, Showing Widespread Nodular Lesions Bilaterally, with Confluence in the Right Lower Lung.*

were seen within this density; the minor fissure was lower than normal. Films of the hands, calvarium, dorsolumbar spine and pelvis were normal.

Bronchoscopic examination showed a considerable amount of watery, clear secretion in both main bronchi; all the bronchial orifices appeared normal; there was a moderate amount of mucosal injection. The patient was discharged without specific therapy on the sixth hospital day.

Second admission (three months later). In the interval he continued to cough up copious quantities of watery sputum. X-ray films of the chest six weeks before entry demonstrated further spread of the lesions throughout the left-middle-lung and left-lower-lung fields. From the sixth to the third week before admission the right lower lung was irradiated with 3000 r. During the three weeks before entry he noted increasing dyspnea on exertion. Films of the chest three days before admission demonstrated slight clearing of the mottled density in the right lower lung; no definite change was noted in the left lung.

Physical examination showed dullness and egophony at the right lung base. Moist rales were audible at both lung bases, especially on the right side.

The temperature was 102°F., the pulse 86, and the respirations 16. The blood pressure was 130 systolic, 90 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 15.4 gm. per 100 ml. and a white-cell count of 7800. The alkaline phosphatase was 5.4 units.

A course of nitrogen-mustard therapy was given. The patient was discharged on the third hospital day at which time the temperature was 101°F.

Third admission (two months later). During the interval there was no improvement in symptoms. X-ray films of the chest six weeks before entry demonstrated an increase in the infiltration at the right-lung base. Subsequent films showed further progression of the infiltration in the right lower lung, displacement of the mediastinum to the right and elevation of the right leaf of the diaphragm (Fig. 2).

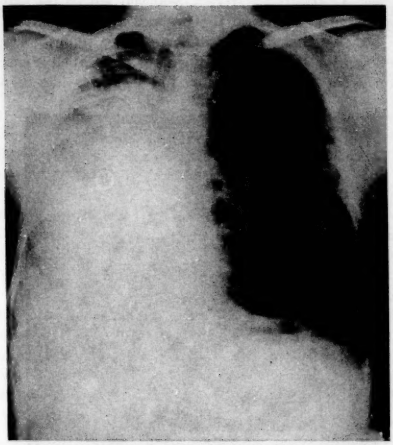

FIGURE 2. *Roentgenogram of the Chest Nine Weeks after Radiation.*
There is extensive collapse of the right lung, with a shift of the mediastinum to the right.

Two days before entry there was an episode of severe coughing that was associated with sudden pain in the right side of the chest anteriorly and increasing dyspnea. The pain, which was accentuated with deep breathing and movement, persisted.

Physical examination showed a well nourished man in slight distress who was breathing with rapid, short respirations. The trachea was shifted slightly to the right. Examination of the chest revealed diminished to absent breath sounds over the entire right lung. Basal rales were audible on the left.

The temperature was 99°F., the pulse 80, and the respirations 26. The blood pressure was 124 systolic, 84 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 14.2 gm. per 100 ml. and a white-cell count of 9300. The nonprotein nitrogen, the total protein, the albumin and the globulin were normal. X-ray films of the chest (Fig. 3) demonstrated a hydropneumothorax on the right, with al-

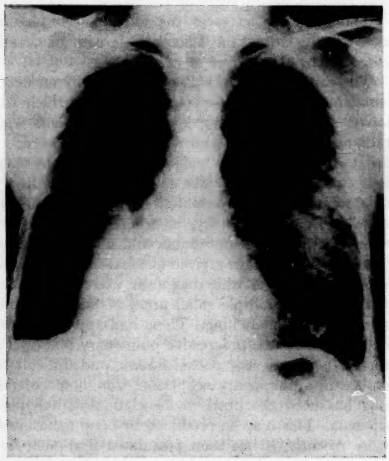

FIGURE 3. *Roentgenogram of the Chest, Showing a Massive Pneumothorax on the Right Side.*
A bleb is visible in the right apex. The pulmonary lesions on the left are more extensive.

most complete collapse of the right lung; the fluid level was at the eleventh rib posteriorly; the left lung was poorly expanded and contained multiple small, flocculent calcifications.

A thoracentesis on the right yielded 5500 ml. of air. Films of the chest on the fourth hospital day showed no change except for a slight increase in pleural fluid on the right in spite of pleural catheterization and suction. On the next day x-ray films of the chest demonstrated slight expansion of the right lung with about the same amount of pleural fluid as previously noted; widespread infiltration of the left lung was seen; air was present in the pectoral muscles. Subsequently, subcutaneous emphysema extended to the face, the forearms and the inguinal regions. Swallowing became difficult. X-ray films of the chest revealed persistent collapse of the right lung and emphysema that encircled the thoracic cage.

On the ninth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. KENNETH T. BIRD*: The findings during the first admission certainly support a diagnosis of carcinoma of the lung, most probably of the alveolar-cell variety, which is now called bronchiolar carcinoma. I shall not trace the relation of this type of carcinoma to so-called jagziekte disease of sheep, since everyone else does when this subject is mentioned. The severe cough productive of large quantities of clear mucoid sputum, the diffuse findings in the x-ray films and the tumor cells found in the sputum are all consistent with this diagnosis, as are the bronchoscopic findings, which were essentially normal.

But this is not the only diagnostic possibility. On the basis of the data I can also think of the various granulomatous diseases, noninfectious and infectious, including fungous diseases. A negative histoplasmin skin test, for example, does not exclude the possibility of active histoplasmosis. Fungous skin tests are often misleading, since they may be negative in the presence of proved active infection. This is especially so of histoplasmosis and blastomycosis. On the other hand, in view of the negative full-strength PPD test, I should exclude tuberculosis — especially since I shall assume that the tuberculin was freshly prepared.

Metastatic pulmonary neoplasm must be considered. Although the lungs may be secondarily involved by neoplasm via either the systemic circulation or from the abdominal viscera through the portal vein and liver, I find nothing to indicate an extrapulmonary source of metastases.

Up until now I have assumed that the sputum was indeed positive for malignant cells "consistent with adenocarcinoma." Could this report have been an overstatement? This is possible but not likely. It is not necessary to consider that the finding of exfoliated tumor cells in the sputum is the result only of a primary neoplasm. The primary source could be in the gastrointestinal tract, the genitourinary tract and so forth, to mention a few of the most likely extrapulmonary sites, but there is no evidence for an extrapulmonary neoplasm.

Thus far I have had only a description of the x-ray findings. Perhaps the visual image itself would be more helpful. May I see the films now?

DR. JOSEPH HANELIN: These films were selected from examinations that extended over approximately a five-month interval. The first films of the chest show widespread disease in both lungs, with multiple nodules that vary in size from a few millimeters up to about 1 cm. and in areas are confluent (Fig. 1). The confluence of these densities is particularly apparent in the right lower lobe, which seems to be somewhat reduced in size. There is obvious progression of the process from the first examination to the films taken approximately six weeks later and again about three

*Assistant in medicine, Massachusetts General Hospital.

months later. At this point irradiation was given to the right lower lung. A good-sized field was employed. The description of an irradiated field 20 by 15 cm. given in the record might almost have covered the entire right lung. The lesions have partially cleared about four to six weeks after treatment was terminated; there seems to be a lesser amount of involvement of the right-lower-lung field. The lesions on the left are about the same or perhaps slightly less in extent. About two months after treatment was terminated, however, there is evidence of progressive collapse of the right lung, with shift of the mediastinal structures to that side and almost total opacity of the lower two thirds of the right-lung field (Fig. 2). Then followed the episode of pain and the appearance of the hydropneumothorax (Fig. 3). After irradiation of the lung we may or may not see this sequence of events with the marked amount of collapse that this patient showed. It is likely that the radiation played some part in the development of the consolidative atelectatic process. I think we are visualizing a bleb or two in the right apex of the collapsed lung. A few days later there is some re-expansion of the collapsed lung in its upper portion, where presumably the radiation was not given. The disease in the left lung has progressed during the time we are speaking about.

DR. BIRD: Was a barium-swallow examination done, and did it show any abnormality?

DR. HANELIN: I do not remember. I do not think any comment was made about it.

DR. BIRD: The protocol states that there was no evidence of an extrapulmonary primary neoplasm.

DR. HANELIN: I saw none.

DR. BIRD: Was there any evidence of hypertrophic osteoarthropathy in the long bones?

DR. HANELIN: No; I saw no such changes.

DR. BIRD: Was there any diffuse decalcification?

DR. HANELIN: There was no decalcification.

DR. BIRD: I should like to be sure that the patient's occupation was just that of a laundry worker. Was there any other occupational history?

DR. BENJAMIN CASTLEMAN: Not so far as I know.

DR. BIRD: The second admission was prompted by increasing dyspnea, which occurred after irradiation. He had received 3000 r over a twenty-one-day period. Was this supervoltage therapy?

DR. HANELIN: Yes.

DR. BIRD: I ask because this technic allows more extensive depth radiation than previously available methods do, and may lead to more damage to underlying tissues.

Only three days before the second admission slight clearing was noted at the right base on the film of the chest. This is somewhat against the impression that I had from reading the abstract that a radiation pneumonitis was present.

Fortunately for me, I can point out that the appearance of the x-ray changes in radiation pneumonitis may occur suddenly days or weeks after the course of irradiation. The finding of egophony at the right base during the second admission is of clinical interest and points to continuing patency of the bronchial tree with parenchymal consolidation. Despite the temperature of 102°F. the white-cell count was normal. Hence, associated infection seems remote. The febrile nature of radiation pneumonitis is presumably caused by the severe necrotic inflammatory changes produced by the radiation.

The slight elevation of the alkaline phosphatase noted at this admission is compatible with metastatic involvement of the liver or of the bone.

The third admission was precipitated by an acute spontaneous pneumothorax on the right, which followed a severe coughing spell. Most patients with radiation pneumonitis and fibrosis have a degree of organizing pneumonia, and some have emphysematous changes. I should like to postulate the rupture of a subpleural emphysematous bleb, or more likely a bulla, brought about by the severe coughing spell, with a resultant pneumothorax and pleural effusion.

At this point I have arrived at what may be a most important aspect of this diagnostic exercise, the first description of multiple small areas of flocculent calcification in the left lung. These had apparently developed during the progressive pulmonary illness. To me this is a most unexpected finding and difficult to explain in a pulmonary neoplasm. Carcinoma of the lung has been described in association with hypercalcemia. This may be produced by bony metastases. More recently, it has been postulated that such hypercalcemia may be caused by excessive bone resorption, secondary to substances introduced into the circulation by a primary neoplasm of the lung.* I should then have to assume that metastatic calcification within the lungs resulted from the hypercalcemia. Perhaps this is why the alkaline phosphatase was elevated. As Dr. Hanelin has implied, there may be some difference of opinion about the extent or even about the presence of calcification.

DR. HANELIN: I suspect that there were no calcium deposits in the nodules. It is difficult to be sure, because the nodules do look somewhat dense in some of the films; in part, the appearance may be the result of the technic employed.

DR. BIRD: The presence of calcification described in the protocol made me wonder about a diagnosis of pulmonary alveolar microlithiasis or calcinosis of the lungs. In this disease progressive dyspnea and the production of large amounts of clear, mucoid sputum are featured. The end state of the disease is characterized by complete destruction of the alveolar walls, with both marked fibrosis and laminated microliths within the alveoli. The early stages may well be characterized by alveolar fluid formation.

*Thomas, W. C., Jr., and Howard, J. E. Etiology of hypercalcemia associated with lung carcinoma. *J. Clin. Investigation* 35:697, 1956.

Bronchiolar carcinoma, a most controversial type of neoplasm, ordinarily does not calcify, although I have happened upon a single case report in which calcification preceded by fourteen years the development of a bronchiolar carcinoma; the calcific deposits were found in the mucuslike excretions of the tumor.

Another possibility — if there was calcification — is to suggest that the protein-rich exudate of radiation pneumonitis somehow allowed deposition of calcium within the lung tissue. Aberrant or metastatic calcification has a predilection for the stomach, kidneys and lungs, possibly because of the relative alkalinity of the parenchymal tissues. But this is sheer speculation.

I do not believe that there was an associated infectious process with caseation or coagulation necrosis and resultant calcium deposition, such as might occur in tuberculosis, histoplasmosis and similar infections.

To summarize, the most likely diagnosis is carcinoma of the lung, probably of the bronchiolar variety. This was complicated by radiation pneumonitis and fibrosis. Much of the architecture of the neoplasm in the right lung may have been obliterated by irradiation. Then, a right-sided tension pneumothorax due to rupture of an incidental bulla complicated by extensive subcutaneous emphysema developed. The operation may have been a thoracotomy, with catheter drainage, to relieve the dyspnea and difficulty in swallowing. Finally, although I cannot be convinced that "flocculent calcification" was present, perhaps the roentgenologist was indeed omniscient, since much of the metastatic calcification of the lungs demonstrated by the pathologist in the microscopical sections goes unrecognized by the somewhat more gross technic of radiology.

Clinical Diagnosis

Carcinoma of lung, bronchiolar type.

Dr. Kenneth T. Bird's Diagnoses

Carcinoma of lung, bronchiolar type.
Radiation pneumonitis and fibrosis.
Rupture of bulla, with pneumothorax.

Anatomical Diagnosis

Bronchiolar carcinoma (pulmonary adenomatosis).

Pathological Discussion

Dr. Castleman: Dr. Waddell, you followed this patient before operation; do you have any comment?

Dr. William R. Waddell: We treated this patient with the same diagnosis that Dr. Bird has arrived at. The worst feature of this disease is the fact that there is nothing the physician can do. Part of our efforts were carried out with this in mind. We treated the patient with cortisone for a while, without any effect; then, we instituted the radiation while he was still receiving cortisone, with the idea that perhaps the inflammatory effect of the radiation might be inhibited. We actually entertained the possibility of irradiating both lungs if this treatment turned out well. It did not; he had been bothered a great deal by the radiation, and, furthermore, the tumor had not responded to the treatment. The cortisone, which he received over a period of many months to the time of the operation, did have one effect that could be accurately measured — that was, the reduction in the sputum from up to a pint a day to 2 or 3 ounces a day. This was gratifying to him. Of course, he had the usual euphoria that often accompanies the administration of cortisone.

Figure 4

Dr. Reed Harwood: I should like to ask if there was more than one positive report of the cytology of the sputum.

Dr. Waddell: There were seven consecutive positive reports.

Dr. Castleman: The operation was a pneumonectomy. Why was a pneumonectomy advised?

Dr. Waddell: Actually, nothing was advised before the operation. It was carried out by Dr. Robb H. Rutledge with the intention of exploring and doing what could be done. At operation the lung was totally collapsed except for a small area of aeration at the apex. A hole in the upper lobe could be visualized at the point of leakage. It was not in a definite bleb but was surrounded by tumor tissue, which was stiff and hard. I am sure that the area that showed on the film was the point of leakage. Since we could not close the hole by a suture, and since the hilus, although indurated and full of inflammatory tissue, contained no metastatic disease that would prevent resection of the lung, we performed a pneumonectomy. I think the wisdom in

our doing that procedure has been borne out by what has happened to the patient: the breathing difficulty has been considerably relieved; the sputum is of small amount; and the disease has been palliated to a remarkable degree.

DR. CASTLEMAN: In other words, most of the symptoms before operation were caused by the pneumothorax.

FIGURE 5

DR. WADDELL: Yes.

DR. CASTLEMAN: The right lung, except for a small part of the upper lobe, which was aerated, showed what looked like a solid lobar pneumonia. The gross appearance was not that of cancer; it was shiny rather than granular (Fig. 4). This is what is expected in adenomatosis, or what probably should be called bronchiolar carcinoma, as Dr. Bird has indicated. The lung retains its shape; it does not collapse at all and has the appearance of the gray hepatization of lobar pneumonia. Microscopically, there was a papillary arrangement of the tumor cells that lined each alveolus, which is believed by most authorities to be an extension from the bronchiole. The individual cells were not atypical, and there were very few mitoses. The tumor did not cross the interlobar or interlobular septums — another common finding in bronchiolar carcinoma. It is believed that the diffuse character of the disease is caused by aspiration or embolization via the respiratory tracts, rather than direct extension across septums.

DR. HANELIN: Was there anything that might be attributed to radiation?

DR. CASTLEMAN: No; I do not believe so. A very interesting observation in view of the discussion about the calcification is that in many areas there were foci of calcification just like the psammoma bodies that we often see with papillary tumors of the ovary, thyroid gland and so forth (Fig. 5). It is the first time that I have seen it in this condition. Whether this is an early stage of microlithiasis, which would look somewhat like this but, of course, without the tumor, or whether it was the type of calcification seen in papillary tumors, I do not know. I suppose it may have been related to the irradiation.

DR. HANELIN: Was the calcification diffuse?

DR. CASTLEMAN: We found it in many areas. The regional lymph nodes, as is usual in these cases, were completely free from metastases, and there was no disease in the major bronchi. So that this is a characteristic example of bronchiolar carcinoma or pulmonary adenomatosis.

DR. HARWOOD: What is the prognosis?

DR. CASTLEMAN: According to the reports in the literature, patients have lived six or seven years after this degree of involvement; but most of them live about two years. We have often seen involvement of one lobe, then of one lung and finally of the opposite lung, all within a period of two or three years.

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FALL MEETING OF THE COUNCIL

THE stated fall meeting of the Council of the Massachusetts Medical Society was held in John Ware Hall of the Boston Medical Library on October 3, 1956; 246 of the 409 councilors were present.

The first half hour or more of the Council's time was given over to a prolonged debate regarding the fiscal relations between the Massachusetts Medical Society and the Boston Medical Library. Since the Council apparently approved by a large majority the support given by the Society to the Library when a vote was finally taken, it appeared that the present generous policy, recommended by the Committee on Finance, is considered to represent one of the most useful and entirely unselfish functions that the Society performs.

A resolution providing that the Council of the Society should implement the introduction and sponsoring of legislation in the General Court of the Commonwealth designed to outlaw medical fee splitting had been disapproved by the Committee on Public Relations and the Executive Committee. The Council upheld this decision of its committees despite an opinion handed down by the Supreme Court of Ontario, Canada, labeling fee splitting as illegal in that province. A strong body of general opinion seems to be that laws should not take the place of conscience on such matters of right or wrong and cannot satisfactorily settle issues of moral behavior.

The Committee on Public Relations had also considered a communication sent to this society from the Blair County Medical Society of Pennsylvania, presenting a resolution disapproving the action of the Council on Medical Education and Hospitals of the American Medical Association relative to the intern matching plan as it affects small hospitals. The tenor of the resolution indicated that the small hospitals were being arbitrarily and unfairly treated, and the Committee on Public Relations recommended that the Council of this society take similar action. However, the timely explanation by Dr. Faulkner, of Norfolk, a member of the Council on Medical Education and Hospitals, led to the tabling of the recommendation.

A question was raised regarding the propriety of the council of a state society receiving and acting on a resolution of this nature presented by the county or district society of another state.

In a consideration of the report of the Committee on Welfare Problems, a rough time, as was expected, was had by all, much of the discussion revolving around the question whether welfare payments should go direct to the attending physician or to the patient, to be forwarded by him to the doctor, when, as and if. At this point the piling of amendment upon amendment resulted in an intricate parliamentary puzzle that left the councilors still in attendance in a state of physical defeat and intellectual frustration. With no

reflection being cast on the purposes of democracy or any suggestion made that the technic of cloture be substituted for prolonged, intelligent and vigorous debate, it has seemed to some observers that the occasional confusion, backtracking and noncontributory oratory with which the Council is visited might be reduced to a reasonable minimum.

Not a few of the councilors are relatively unacquainted with and genuinely uninterested in the finer details of parliamentary procedure. They are moreover primarily physicians, distinguished above the average in their communities, who are ungrudgingly giving their time to their fellows from their usually pressing duties. It may be that they should be spared those long and frequently fruitless debates from which their executive committee was intended partly to relieve them, or be furnished with some thread to guide them safely out of the Cretan labyrinth into which the complicated workings of the human mind has thrown them.

It may be that a professional parliamentarian on the platform would be of service. Without in any way affecting the length, the number or the brilliant reasoning of the arguments presented, he might at least save the Council valuable time by unraveling the snarls that sometimes get into its knitting.

MASSACHUSETTS INSTITUTE OF LABORATORIES

In Chapter 92 of the *Resolves* of 1956 the Massachusetts legislature authorized and directed the Department of Public Health to study the needs of the Institute of Laboratories. The *Journal* believes that this step should meet with more than silent approbation and that the medical profession of the State should know of and commend this effort.

For some years diagnostic facilities on the State level have not been able to keep pace with the growth of knowledge in this field or with the increasing needs of an expanding population. Both in personnel and in facilities the work has increased beyond present capacity. This is particularly true of diseases caused by viruses and fungi.

Massachusetts began diagnostic bacteriology in 1895 under the leadership of Dr. Theobald Smith. Research in those early days played a prominent part in the work of the laboratory and in the improvement in diagnostic methods. From that early beginning until the present the State laboratories have enjoyed the sustained interest of the Harvard Medical School. Dr. Smith, in an address at the Harvard Club, June 2, 1915, on the eve of his leaving to establish the Animal Pathology Laboratories for the Rockefeller Institute, made reference to this. At that time he said, "You may or may not know that the State Board of Health was the guest of the Bussey Institution for over nine years, for during this time it was housed, it was warmed, had its janitor service and I think was illuminated and watered without pay." He went further to estimate that Harvard had saved the State between $30,000 and $50,000.

Although the State is at present more or less of a "paying guest," curiously enough, some things have not changed. The bacteriologic and Wassermann diagnostic work is now done in the Bussey building, which was completed in 1872 and has had but few alterations since that time. For the Bacteriologic Laboratory this is a return to the scenes of its birth after an extended sojourn in the State House. For the Wassermann Laboratory it has meant moving from Harvard quarters at the Medical School, where it was first established in 1915, to the Harvard Bussey property. Although there is no doubt that strong bonds must always be maintained between the State laboratories and the medical schools, teaching hospitals and the entire medical community, it seems that after more than sixty years of tenancy the State would be well advised to consider ownership of such an important group of laboratories. In this manner the needs for expansion, as health needs and knowledge dictate, can be served better.

Through the wisdom and leadership of the Massachusetts State Board of Health, the Commonwealth learned early the use and value of good public-health laboratory facilities. It does not seem too much to expect that such facilities keep pace with the present and future needs under the guidance of the Department of Public Health and the enlightened medical community hereabouts.

REHABILITATING THE SIGHTLESS VETERAN

An encouraging and inspiring adventure in rehabilitation has been recounted in a recent release by the Information Service of the Veterans Administration. Related to the totally blinded veterans of World War II and the Korean conflict, the study discusses the varied occupations that have been successfully entered by 388 of those so handicapped.

Listed among them are a veteran who now heads the speech department of a large college, teaching eleven hours a week and spending another forty-five hours in preparing lessons, in addition to which he manages the college debating team. Another is a trial lawyer who has won election to the legislature of his state and a third is an instrument maker.

Taken as a group these veterans have tended to avoid sedentary occupations rather than to concentrate in them, and some have entered fields that have not before been attempted by blind persons. Percentage-wise the greatest number — 38 per cent — are occupied in the professions, technical work and management. Fourteen per cent are clerks and salesmen, 13 per cent are farmers of one sort or another, 10 per cent are mechanics in fields requiring a high

degree of technical skill, and 25 per cent are performing manual work of a less highly skilled order.

More specifically, the group includes teachers up to professorial grade, journalists and other writers, editors, a concert singer, a clergyman, a YMCA executive secretary, a biologist in the United States Fish and Wildlife Service, a government economist in international affairs, and 2 chiropractors. One is a binder of rare books, 3 are cabinetmakers, others repair radios, operate looms and sell a variety of goods. One repairs bicycles, another overhauls automobiles and still a third is a grinder of lenses. Although the operation of vending stands is a favored occupation among those who have not acquired intellectual training or technical skills, not one is listed as selling pencils on the street.

Most of the veterans included in the survey, according to the report, had received vocational rehabilitation training under Public Law 16.

BEARING GIFTS

First fruits of the Ford Foundation's $90,000,000 appropriation, made last December to aid the instructional programs of the country's private medical schools, were distributed in September of this year. According to an announcement of the Foundation at the time, grants totaling $21,750,000 were allocated in sums of $500,000 to each of the 43 four-year schools, including, in New England, those of Boston, Harvard, Tufts and Yale universities, and in the sum of $250,000 to the two-year school of Dartmouth College.

In accordance with the terms of the distribution the grants are to be held by their recipients as invested endowment for at least ten years, the income being used for instructional purposes only, after which the principal also may be expended.

With this noble generosity as an example it may be hoped that some equally enlightened philanthropic establishment will recognize and act upon the needs of such an indispensable institution as the Boston Medical Library. One of the great repositories of the recorded medical knowledge of the ages, it serves faithfully in its unspectacular and inadequately rewarded way the very schools whose needs are being so dramatically met. "They also serve," as a great poet wrote in his physical blindness, "who only stand and wait."

Dr. Baillie, of London, remarked that he had never known a physician, who from any cause, acquired business rapidly in London, who permanently retained it.

Boston M. & S. J. *October 23, 1856*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

Pseudomembranous Enteritis

A twenty-seven-year-old gravida III, para II, with an uneventful prenatal course was admitted to the hospital because of mild, irregular uterine contractions at term. There was no bleeding or other abnormality. After the usual preparation, the patient fell asleep for the remainder of the night. Several hours later, after a few irregular contractions but without any bleeding and with the membranes still intact, the uterus was described as "hard," and the fetal heart tones could not be heard. Pain was not severe enough to require sedation. At this point, approximately twelve hours after admission, a general surgeon, called in consultation, performed a rapid cesarean section with the diagnosis of premature separation of the placenta.

A normal, active, full-term baby was delivered through a lower-segment incision, the placenta being found normally implanted, with no free blood in the uterus.

On the second postoperative day, the temperature rose to 102°F., and persistent vomiting began. In the next few days, during which the patient continued to vomit, the material developed a fecal odor. Simultaneously, diarrhea began. This was steady and did not respond to the administration of penicillin and streptomycin. No cultures were taken. She received intermittent gastric suction but continued to vomit. In the course of eight days she received parenterally a total of 4000 ml. of saline solution, 1000 ml. of glucose and distilled water and one "small" transfusion. There was never any abdominal distention or evidence of pulmonary involvement. According to the nurses, diarrhea poured forth in a constant stream and was foul-smelling and watery. These conditions continued until death on the eighth day. Autopsy revealed findings typical of pseudomembranous enteritis. Post-mortem cultures identified *Escherichia coli* and hemolytic, anaerobic staphylococci. There was no evidence whatsoever of peritonitis or of infection in the reproductive tract, the cesarean scar being well healed.

This case was classified as a preventable death, with responsibility assigned to the physicians. Death was caused by pseudomembranous enteritis. The primary avoidable factor was an unnecessary cesarean section.

This case is discussed separately on obstetric and surgical considerations, in that order.

The patient had had two previous children without difficulty, and there is no apparent reason why she

should not have been able to deliver a third as easily. On admission at term, labor was not yet established, the membranes were intact, and, in fact, there was no bloody show. Consequently, treatment could have been expectant and might have included mild sedation and encouragement. However, the fetal heartbeat was lost, and the uterus was described as "hard." These two data are the only facts to support a diagnosis of premature separation of the placenta, for which the emergency cesarean section was then done. This unfortunate error could have been avoided. Nontoxic premature separation of the placenta is usually, but not always, accompanied by profuse vaginal bleeding. In the absence of vaginal bleeding, the uterus is not merely hard but tetanically contracted and covered by an almost boardlike abdomen, and is excruciatingly tender. The patient is almost invariably in great distress. None of these signs or symptoms were present with this patient. Failure to hear the fetal heart sounds may mean nothing in the diagnosis of a separated placenta and should most certainly not precipitate sudden surgery.

Assuming, however, that the diagnosis had not been mistaken and that, indeed, a separated placenta did exist, the mode of treatment left much to be desired. In general, the conservative treatment for separation of a placenta is rupture of the membranes and encouragement of labor. Cesarean section must, of course, be resorted to when vaginal hemorrhage is severe, in the absence of adequate banked blood or when the procedure described above fails to diminish bleeding and to produce reasonably good labor. In the absence of hemorrhage there is rarely any cause for haste unless it is the often-justified effort to save a baby. It is axiomatic, however, that quick cesarean sections done for the sake of the fetus are justified *only* when there is excellent evidence that the baby is alive and will survive this procedure. In the case at hand, the exact opposite was thought to be true although, to be sure, this later proved erroneous. In other words, in the absence of hemorrhage, a cesarean section is not merely unindicated but also, in fact, *contraindicated* by the absence of a good fetal heartbeat.

So far as the surgical aspects are concerned, granting that errors in diagnosis and management were honestly made, the patient was illogically subjected to a lower-segment cesarean section. Presumably done in haste for the sake of a living child, a classic incision would have been the most expeditious.

But a rare but vicious and usually fatal complication of abdominal surgery developed. This first became apparent on the second and third days, when a fecal odor was noted in the vomitus and diarrhea began. It is not surprising that the patient deteriorated rapidly and died within a week. The mortality from pseudomembranous enteritis is extremely high, those who survive doing so only when they receive the most vigorous and unremitting support, fluid therapy, electrolyte control, transfusions and meticulous nursing care. Antibiotics, although sometimes causative, may have their place, but without the other measures their use is fruitless. In persistent vomiting and diarrhea, copious intravenous infusions of fluids seem to have been indicated, and yet only 4000 ml. of saline solution was given, in addition to a flask of distilled water and one "small" transfusion during seven days. If this record is correct, the inadequacy of the treatment is obvious. Regardless of the outcome, the patient should have received the benefit of rehydration and electrolyte balance.

In summary, this patient died from a usually fatal surgical complication for which she was inadequately treated, after an operation that both in retrospect and in advance was obviously unnecessary. If she had been allowed to go into normal labor and to have her baby in the usual manner without interference, she would probably be alive today since pseudomembranous enteritis is unknown after normal pelvic deliveries.

JOHN FIGGIS JEWETT, M.D.
Chairman

DEATH

NADEL — Samuel Nadel, M.D., of Dorchester, died on September 10. He was in his sixtieth year.

Dr. Nadel received his degree from Tufts College Medical School in 1920. He was formerly deputy commissioner of health for the city of Boston and staff member at Harley Hospital, Dorchester, Allerton Hospital, Brookline, and Boston City Hospital.

He is survived by his widow and a daughter.

CORRESPONDENCE

AMERICAN CANCER SOCIETY

To the Editor: During the annual meeting of the American Cancer Society, scientific sessions devoted to a symposium on the relations between endocrines and cancer will be held on October 29-30 in the Grand Ballroom of the Park Sheraton Hotel, 7th Avenue at 55th Street, New York City.

This program undoubtedly will be of great interest to physicians. The speakers are particularly outstanding in the scientific world for their contributions in the field of hormone-tumor relations and include several from overseas.

All physicians and medical students are invited, and programs may be obtained, on request, from this office.

CLARENCE L. SCAMMAN, M.D.
Medical Director
American Cancer Society
Boston

REVOCATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held September 20, 1956, it was voted to revoke the registration of Dr. Herbert P. F. Corbin, Adams, Massachusetts.

ROBERT C. COCHRANE, M.D., *Secretary*
Board of Registration in Medicine
State House
Boston

BOOK REVIEW

Mechanisms of Congenital Malformation: Proceedings of the second scientific conference of the Association for the Aid of Crippled Children, June 15 and 16, 1954. By S. R. M. Reynolds, M.D.; Harold Wolff; Joseph Dancis, M.D.; and Clement A. Smith, M.D. 8°, cloth, 137 pp., with 50 illustrations and 16 tables. New York: Association for the Aid of Crippled Children, 1954.

This conference was attended by 43 scientists from this country and abroad. The discussions have been carefully edited and indexed, and a bibliography appended.

The first part of the discussion concerns the physical, chemical and sociologic aspects of the fetal environment. The second discusses the placental barrier and its possible selective action in holding back certain substances and allowing others to pass, and the third considers three aspects of fetal development: the blood-brain barrier; the fetal adrenal glands; and fetal respiration.

The material should be of interest to everyone concerned with the problems of the premature and full-term newborn infant.

JAMES M. BATY, M.D.

NONCLINICAL NOTES

WOMAN'S AUXILIARY TO MASSACHUSETTS MEDICAL SOCIETY

At the fall conference and executive-board meeting of the Woman's Auxiliary to the Massachusetts Medical Society Dr. Samuel B. Kirkwood, Massachusetts Commissioner of Public Health, spoke on the subject "The Auxiliary and Public Health." Dr. Ruth Beaucher, director of the Children's Unit of the Metropolitan State Hospital, gave a talk entitled "The Psychotic Child." A Norfolk District member, Mrs. David L. Halbersleben, discussed the Hoover Report. Films on safety and health careers were shown as part of the program.

Special guests at the meeting included Dr. Howard F. Root, president of the Massachusetts Medical Society; Dr. Paul F. Bergin, president of the Worcester District Medical Society; Dr. John F. Conlin, chairman of the Medical Society Advisory Committee to the Auxiliary; and Mr. Everett C. Spencer, Jr., director of public relations of the Massachusetts Medical Society.

DR. SOSMAN HONORED

Dr. Merrill C. Sosman, who retired this year as professor of radiology at Harvard Medical School and radiologist at the Peter Bent Brigham Hospital, was awarded the gold medal of the American Roentgen Ray Society at its annual meeting in Los Angeles on September 27. The award was made for Dr. Sosman's studies that revealed the nature and progression of pulmonary alveolar microlithiasis.

NOTICES

ANNOUNCEMENT

Dr. John J. Sullivan announces the opening of an office at 9 Central Street, Lowell, Massachusetts, for the practice of ophthalmology.

POSTGRADUATE MEDICAL INSTITUTE

The Postgraduate Medical Institute, operating under the sponsorship of the Massachusetts Medical Society with the collaboration of Boston University School of Medicine, Harvard Medical School, Harvard School of Public Health, Tufts University School of Medicine, Massachusetts Chapter of the American Academy of General Practice, Massachusetts Department of Public Health, the Lahey Clinic, the Joslin Clinic, Massachusetts Division of the American Cancer Society, Incorporated, Massachusetts Chapter of the Arthritis and Rheumatism Foundation, Boston Tuberculosis Association, Massachusetts Heart Association, Incorporated, and the United Cerebral Palsy Association of Massachusetts, Incorporated, has announced its offerings of courses in general medicine for the impending season.

Courses, which are open to all physicians, will be held in Boston at the Lemuel Shattuck Hospital, October 10, 1956, through April 24, 1957; in Worcester at Fairlawn Hospital and Worcester Hahnemann Hospital, January 30 through April 3, 1957; in Holyoke at the Holyoke Soldiers' Home, October 5 through December 14, 1956; in Lynn and Salem at the Lynn and Salem hospitals, January 9 through March 27, 1957; in Lowell at St. Joseph's, St. John's and Lowell General hospitals, October 10 through November 28, 1956; in New Bedford at St. Luke's Hospital, October 3 through December 19, 1956; in Providence at St. Joseph's Hospital, October 3 through November 14, 1956; and in Brockton and Weymouth at the South Shore Hospital, Weymouth, and the Veterans Administration Hospital, Brockton, October 3 through December 19, 1956.

Registration and requests for information regarding all courses should be addressed to Postgraduate Medical Institute, 30 Fenway, Boston 15, Massachusetts.

MASSACHUSETTS SOCIETY OF ANESTHESIOLOGISTS

A meeting of the Massachusetts Society of Anesthesiologists will be held at the Harvard Club of Boston on Friday, November 2, at 4 p.m.

The program will include a round-table dinner discussion. After dinner Dr. Sol Hershey will give a talk entitled "The Role of Anesthesia in the Regulation of Circulation."

AMERICAN CANCER SOCIETY

The annual meeting of the American Cancer Society will be held in the Grand Ballroom of the Park Sheraton Hotel in New York City on October 29 and 30, 1956.

As noticed in Dr. Scamman's letter, published elsewhere in this issue of the *Journal*, the scientific sessions will consist largely of a symposium on the relation between cancer and the glands of internal secretion.

Further information may be obtained from the American Cancer Society, 521 West 57th Street, New York 19, New York, or from the Massachusetts Division, 138 Newbury Street, Boston 16, Massachusetts.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 19–26. New York Academy of Medicine. Page 304, issue of August 9.

OCTOBER 19–31. Consultation Clinics for Crippled Children in Massachusetts. Page 626, issue of September 27.

OCTOBER 19 and DECEMBER 14, 1956, and FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.

OCTOBER 19, 1956–APRIL 27, 1957. Postgraduate Medical Institute. Notice above.

OCTOBER 23. Boston City Hospital House Officers' Association. Page 728, issue of October 11.

OCTOBER 24. Association on Alcoholism. Page 728, issue of October 11.

OCTOBER 24. New England Pediatric Society. Page 731, issue of October 11.

OCTOBER 29. University of Virginia. Page 627, issue of September 27.

OCTOBER 29 and 30. American Cancer Society. Notice above.

OCTOBER 30 and 31 and NOVEMBER 1. New England Postgraduate Assembly. Page 729, issue of October 11.

OCTOBER 31, NOVEMBER 14 and 28 and DECEMBER 12. Walter E. Fernald State School. Page 728, issue of October 11.

NOVEMBER 2. Massachusetts Society of Anesthesiologists. Notice above.

NOVEMBER 4–8. American Institute of Dental Medicine. Page 675, issue of October 4.

NOVEMBER 7–9. American College of Obstetricians and Gynecologists. Page 731, issue of October 11.

NOVEMBER 12–16. American Public Health Association. Page 675, issue of October 4.

NOVEMBER 14–22. Pan-Pacific Surgical Association. Page 490, issue of September 6.

NOVEMBER 18–22. Pan American Medical Association. Page 490, issue of September 6.

NOVEMBER 28–30. American College of Cardiology. Page 731, issue of October 11.

Calendar for the Week Beginning Thursday, October 25

Thursday, October 25

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
8:00–9:00 a.m. Medical Journal Club. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. Open Heart Surgery. Drs. Dwight E. Harken and Warren J. Taylor. Main Amphitheater, Peter Bent Brigham Hospital.

Friday, October 26

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Sulfonylurea Compounds. Dr. Raffael Camerini. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10.00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Medical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*12:00 m. Urologic Conference. Dr. C. J. E. Kickham, presiding. Auditorium, Carney Hospital, Dorchester.
*12:30–1:30 p.m. Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill C. Sosman. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

Saturday, October 27

*8:00 a.m. Clinicopathological Conference. Joslin Auditorium, New England Deaconess Hospital.
*8:00 a.m. Lahey Clinic Medical Conference. Joslin Auditorium, New England Deaconess Hospital.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*9:00–10:00 a.m. Anesthesiology Conference. Dr. Benjamin Etsten. Anesthesia Laboratory, New England Center Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

Monday, October 29

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Tumor Conference. Dr. C. C. Lund and members of the Tumor Board. Dowling Amphitheater, Boston City Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.
*3:00–4:00 p.m. Neuroradiologic Conference. Dr. Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Neurologic Complications of Anesthesia. Dr. Thomas K. Burnap. Surgical Conference Room, Peter Bent Brigham Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Dr. Benjamin Etsten. Stearns Auditorium, New England Center Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Spinal Anesthesia. Dr. Robert B. Orr. Joslin Auditorium, New England Deaconess Hospital.
5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. Edward T. MacMahon. Stearns Auditorium, New England Center Hospital.
*7:00–9:00 p.m. Anesthesia Teaching Conference of Greater Boston. Anesthesia for Traumatic Surgery and Emergency Surgery. Dr. Branch. Auditorium, Jimmy Fund Building, 35 Binney Street.

Tuesday, October 30

New England Postgraduate Assembly. Hotel Statler, Boston.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Medical Grand Rounds. Main Conference Room (Ground Floor), Lemuel Shattuck Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Hematology Conference. Dr. Mario Stefanini. Saint Elizabeth's Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetric). Faulkner Hospital.

Wednesday, October 31

New England Postgraduate Assembly. Hotel Statler, Boston.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. Deaconess II, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. New Facts about Multiple Sclerosis. Dr. Leo Alexander. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry Conference. Drs. John F. Sullivan, Justin Hope and Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Medical-Surgical Rounds. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*4:00–6:00 p.m. Postgraduate Seminar in Pediatric Neuropsychiatry. Research Laboratories, Walter E. Fernald State School, Trapelo Road, Waltham.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*6:30 p.m. Lahey Clinic Lecture. Panel Discussion. Arthritis. Drs. Frank P. Foster, Elmer C. Bartels, Howard R. Crawford and Robert E. Wise. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.